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**New Reactions and Solid Phase Methods for the
Synthesis and Use of Boronic Acids**

by

Kimberley Anne Thompson



A thesis submitted to the Faculty of Graduate Studies
and Research in partial fulfillment of the requirements
for the degree of Masters of Science.

Department of Chemistry
Edmonton, Alberta
Fall, 2001

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled New Reactions and Solid Phase Methods for the Synthesis and Use of Boronic Acids submitted by Kimberley Anne Thompson in partial fulfillment of the requirements for the degree of Master of Science.

Abstract

Boronic acids possess significant biological, medicinal and synthetic applications. Herein, *N,N*-diethanolaminomethyl polystyrene (DEAM-PS) is shown as a valuable solid support to facilitate the derivatization of functionalized boronic acids. This resin has led to the synthesis of many new boronic acids that are not otherwise easy to obtain using solution phase methods. UV spectroscopic studies indicated that boronic acid immobilization and cleavage occur under a rapidly reached equilibrium. The DEAM-PS boronate linkage is stable to a wide range of chemistries under anhydrous conditions. Numerous boronic acid derived amines, anilides, and ureas can be synthesized. Multi-component and sequential reactions are also possible. DEAM-PS supported boronic acids can further be employed in a borono-Mannich resin-to-resin transfer reaction (RRTR) yielding arylglycine derivatives.

A solution phase methodology for the first report of an intramolecular Petasis borono-Mannich reaction has shown promising results. Cyclization with glyoxylic acid is possible for the formation of a six-membered ring product.

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To Grampy Joe and Nan

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List of Abbreviations

Ac ₂ O	acetic anhydride
AcOH	acetic acid
AM-PS	aminomethyl polystyrene
Anal.	elemental analysis
APT	attached proton test
Ar	aryl
Aq	aqueous
BB	broad band
Bn	benzyl
BNCT	boron neutron capture therapy
BOC	<i>tert</i> -butoxycarbonyl
BOC-Gly-OH	<i>N</i> - α - <i>tert</i> -butoxycarbonyl-glycine
br	broad
Bu	butyl
<i>i</i> -Bu	isobutyl
BuLi	<i>n</i> -butyllithium
<i>n</i> -Bu ₄ NI	<i>n</i> -tetrabutylammonium iodide
<i>n</i> -BuOH	<i>n</i> -butanol
°C	degree Celsius
calcd	calculated

δ	chemical shift in parts per million downfield from TMS
d	doublet
DCC	dicyclohexylcarbodiimide
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DEAM-PS	<i>N,N</i> -diethanolaminomethyl polystyrene
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
ee	enantiomeric excess
EI	electron impact
ES-MS	electrospray-mass spectrometry
Et	ethyl
Et ₃ N	triethyl amine
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
exper	experimental

Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
Gly	glycine
h	hour(s)
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
int. std.	internal standard
IR	infrared
<i>J</i>	coupling constant
LRMS	low resolution mass spectrometry
m	multiplet
<i>m</i>	<i>meta</i>
M	molarity
Me	methyl
MeCN	acetonitrile
MeO	methoxy
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitre(s)

mmol	millimole
MS	mass spectrometry
m/z	mass to charge ratio
NaOMe	sodium methoxide
nm	nanometers
NMM	<i>N</i> -methylmorpholine
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
PG	protective group
Ph	phenyl
Ph ₃ P	triphenyl phosphine
pp	polypropylene
ppm	parts per million
<i>i</i> -Pr	isopropyl
psi	pounds per square inch
PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino- phosphonium hexafluorophosphate
q	quartet
qn	quintet
R	alkyl group
rt	room temperature

RRTR	resin-to-resin transfer reaction
s	singlet
sx	sextet
SP	solid phase
SPOS	solid phase organic synthesis
t	triplet
TFA	trifluoroacetic acid
theor.	theoretical
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TMSCl	trimethylsilyl chloride
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
U-4CR	Ugi-four component reaction
μL	microlitre(s)

I. Introduction

Organoboron chemistry dates back more than 100 years and boron compounds have become well established in organic synthesis since that time. This work will focus on new reactions and methods for the synthesis and use of boronic acids, specifically. However, there are several different types of boron containing compounds available as shown in Figure 1.

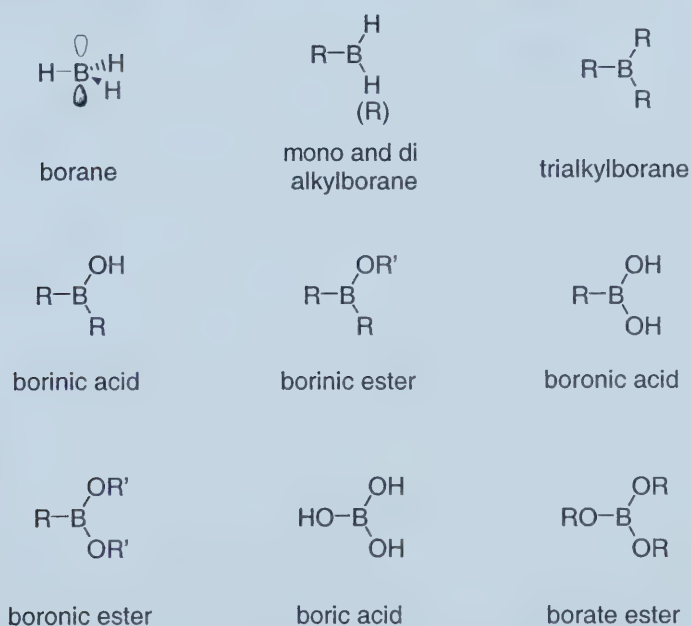


Figure 1. Common boron containing organic compounds

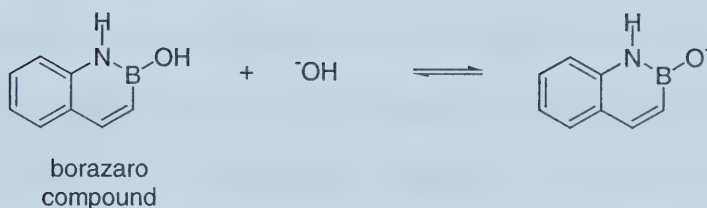
The boron atom in borane is sp^2 hybridized with a vacant p orbital perpendicular to the plane of the three B-H bonds. Thus, borane and its derivatives are electrophilic (Lewis acidic) and are highly susceptible to attack by

a nucleophile. Boronic acids react as Lewis acids, not as protic ones (Scheme 1). They accept a hydroxy anion at high pH in water to form an organoboronate (equation 1). By contrast, a borazaro compound acts as a protic acid (equation 2).¹ This compound does not function as a Lewis acid because the boron is part of an aromatic system, and the aromaticity would be lost upon coordination.

eq. 1)



eq. 2)

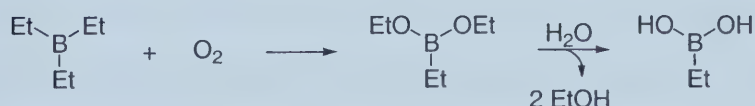


Scheme 1

The generally accepted order of reactivity to oxygen of the following boron containing organic molecules is as follows: $\text{R}_3\text{B} > \text{R}_2\text{BOR}' > \text{RB}(\text{OR}')_2$.¹ The greater the number of boron-oxygen bonds in the alkylboranes the greater the amount of backbonding from oxygen which results in lower Lewis acidity of the boron. Organoborane chemistry is often dictated by the ease of oxidative cleavage of boron-carbon bonds. Boron-carbon bonds are not weak and are

comparable in strength to carbon-carbon bonds. However, boron-oxygen bonds are extremely strong, much stronger than carbon-oxygen bonds. The average energy difference between a boron-carbon bond and a boron-oxygen bond is $\sim 200 \text{ KJ mol}^{-1}$ whereas the average difference between a carbon-carbon bond and a carbon-oxygen bond is only $\sim 25 \text{ KJ mol}^{-1}$.¹ Therefore, thermodynamically, the oxidation of organoboranes proceeds with ease. However, kinetically the oxidation of boronic acids in air is rather slow.

Frankland reported boronic acids as far back as 1862.¹ He obtained the thermodynamically more stable ethylboronic acid after the slow oxidation of triethylborane and the subsequent hydrolysis of the boronic ester formed (Scheme 2). Previously, triethylborane was shown to spontaneously ignite in air and explode in the presence of pure oxygen.¹ Over the years, improvements in the synthesis of organoboronic acids have made them more popular compounds. However, it was not until recently that significant advances for the utility of boronic acids were discovered.

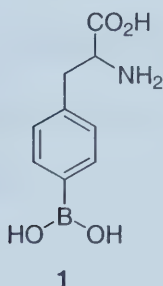


Scheme 2

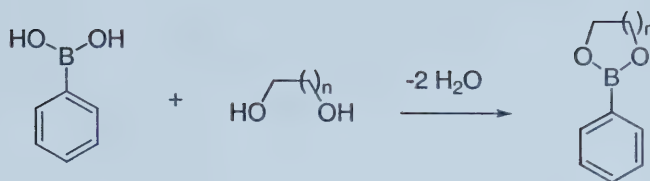
All boronic acids are solids. Most are thermally stable, tolerant to water and oxygen. Boronic acids have relatively low toxicity and environmental impact

when compared to analogous organotin species. Boronic acids can be handled without special precautions making them very convenient reagents to work with. These user-friendly properties have placed a lot of attention on the use of boronic acids in both academic and industrial laboratories.

Boronic acids have significant biological and medicinal applications. For instance, they have shown great potential in boron neutron capture therapy (BNCT) for cancer treatment.² *p*-Boronophenylalanine **1** is a therapeutic agent currently being used in clinical trials in the U.S. for the treatment of brain tumors and metastatic malignant-melanoma in human patients.³



Peptide boronic acids are among the most potent inhibitors of serine proteases,⁴ a large and functionally diverse family of proteolytic enzymes. The ability of boronic acids to react with diols, with the loss of water, to give cyclic boronic esters (Scheme 3) has also led to their application as molecular receptors in carbohydrate recognition⁵ and as selective carbohydrate transporters in lipophilic environments.⁶



Scheme 3

The application of boronic acids in organic synthesis has expanded in the last several years with the discovery of new boronic acid based reactions. Arylboronic acids have become very versatile intermediates leading to a vast array of synthetically valuable molecules such as biaryl compounds,⁷ β -substituted carbonyl compounds,⁸ alcohols,⁹ diaryl ethers,¹⁰ aryl amines,¹⁰ α -amino acids,¹¹ and β -amino alcohols¹² (Figure 2). The reactions depicted in Figure 2 are further discussed below.

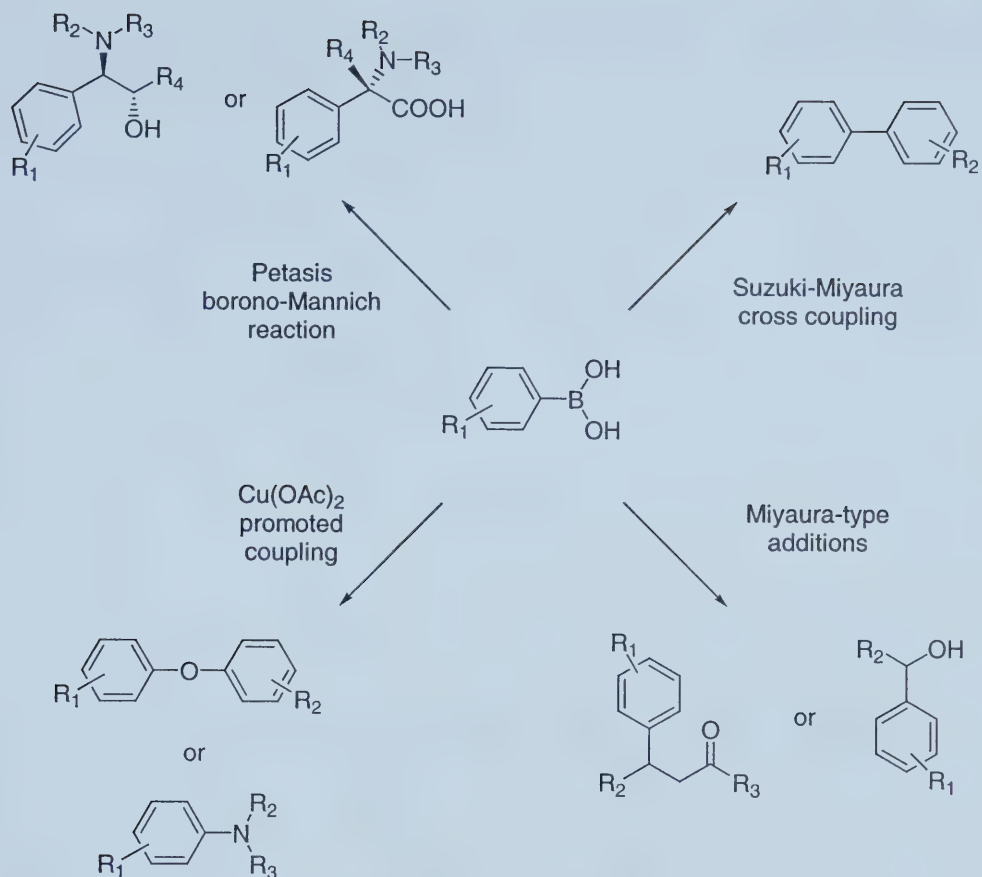
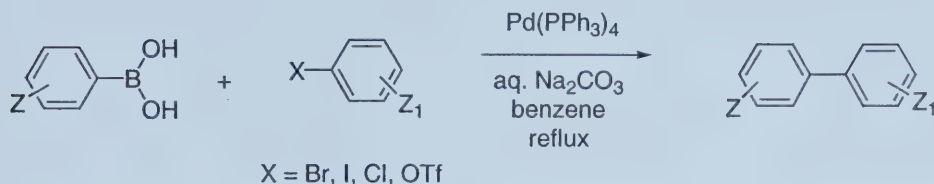


Figure 2. Sample of organic products available via reactions of boronic acids

The Suzuki coupling reaction is probably the most famous example of boronic acid use in synthesis and is regarded in the synthetic community as an extremely powerful tool for carbon-carbon bond formation. Suzuki and Miyaura discovered^{7,13} that arylboronic acids undergo palladium-catalyzed cross coupling with aryl bromides, iodides and triflates in the presence of a base to produce unsymmetrical biaryl compounds (Scheme 4). The reaction has since been

expanded to less reactive but cheaper aryl chlorides¹⁴ and acyl chlorides¹⁵ further increasing its synthetic usefulness.



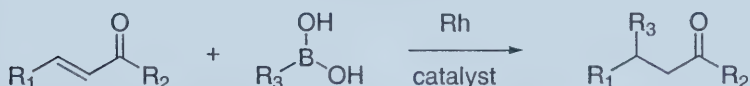
Scheme 4

Organoboronic acids are weakly electrophilic molecules and the organic group on boron is only weakly nucleophilic. However, organoboronic acids are often reactive enough for transmetalation; the transfer of the R group on boron to a transition metal complex. In this case boron must be more electropositive than the transition metal. The result of transmetalation is the formation of a transient nucleophilic species. Boronic acids transmetalate to organopalladium (II) halides (Scheme 5) as a key step in the Suzuki cross-coupling reaction mentioned above.

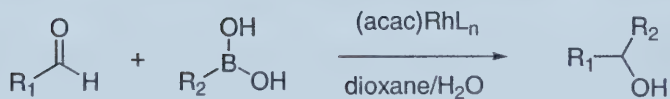


Scheme 5

The discovery of the Suzuki reaction has led to the further development of organic reactions that utilize boronic acids as starting materials. Miyaura and colleagues have recently demonstrated the efficiency of transmetalation from boron to rhodium providing new carbon-carbon bond forming reactions. They have reported the 1,4-addition reactions of organoboronic acids to α,β -unsaturated ketones,⁸ esters,^{9b} or amides^{9b} under rhodium catalysis (Scheme 6). They have also reported the 1,2-addition of organoboronic acids to aldehydes⁹ (Scheme 7) and even imines.¹⁶ Several groups have worked on asymmetric variants of these Miyaura-type addition reactions.¹⁷



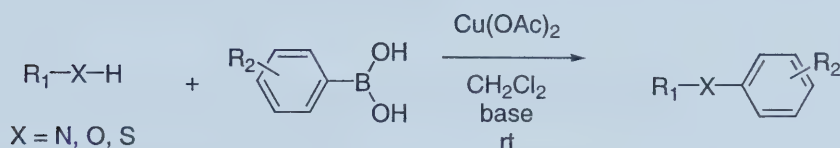
Scheme 6



Scheme 7

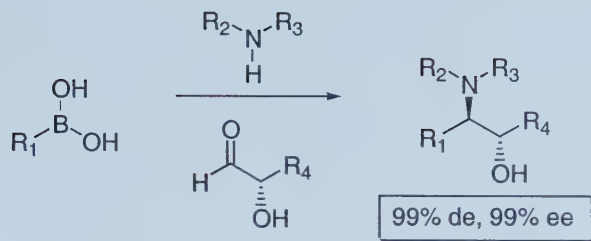
Boronic acids have also been used in forming heteroatom-carbon bonds. Arylboronic acids are efficient arylating agents for N-H,^{10,18} O-H,^{10,19} and S-H²⁰ containing compounds under copper diacetate promoted cross-coupling

conditions as shown in Scheme 8. The $\text{Cu}(\text{OAc})_2$ cross-coupling reaction is successful for the coupling of arylboronic acids to amines,^{10,18b,18c} anilines,^{10,18b} amides,^{10,18b,18c} imides,¹⁰ ureas,^{10,18b} sulfonamides,¹⁰ carbamates,¹⁰ imidazoles,^{10,18a,18d,18e} phenols,^{10,19a,19b,19d} and thiols²⁰ amongst others.^{18a, 18c,19c,} Catalytic variants of this reaction have recently been developed.^{18d}



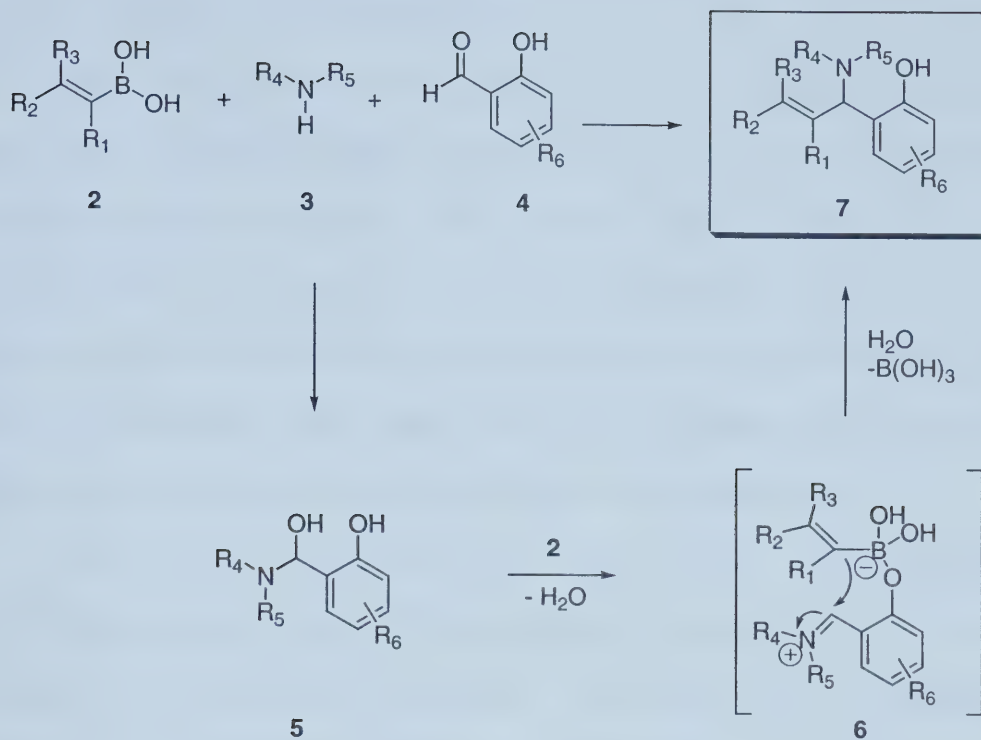
Scheme 8

Petasis has discovered²¹ a three-component variant of the Mannich reaction²² involving the condensation of an organoboronic acid with an amine and certain activated carbonyl compounds such as α -keto acids,¹¹ α -hydroxyaldehydes,¹² (Scheme 9) and salicylaldehydes,²³ leading to α -amino acids, β -amino alcohols and aminophenol derivatives, respectively. As shown in Scheme 9, reactions involving α -hydroxyaldehydes proceed with a high degree of diastereocontrol, forming exclusively the *anti* products in greater than 99% de. Products were obtained with greater than 99% ee when optically pure α -hydroxyaldehydes were used. The three-component borono-Mannich reaction has received much attention in the literature both in solution²⁴ and solid phase chemistry.²⁵



Scheme 9

The Petasis reaction is quite remarkable especially when you consider the usually sluggish reactivity of the boronic acid component. The proposed pathway for the Petasis reaction for the case of salicylaldehyde is shown in Scheme 10.²³ The mechanism presumably involves the initial reaction of the amine and the carbonyl compound to give aminal **5**, which reacts with the organoboronic acid to generate transient species **6**. Transfer of the vinyl group on the boron to the iminium intermediate, followed by loss of boric acid leads to the formation of product **7**. The overall process involves the formation of a carbon-carbon bond at room temperature without a strong nucleophilic species or a catalyst! When the boronic acid takes on the phenol donor group as in species **6**, an electron-rich tetravalent boronate complex is formed. This complex gives the organic vinyl group on the boron enough reactivity to act as a selective nucleophile. Petasis' findings correlate with the known fact that when a negatively charged base coordinates to boron it increases the nucleophilicity of the attached organic group.^{7a} The current major limitation of the Petasis borono-Mannich reaction is that it fails with normal unactivated aldehydes.



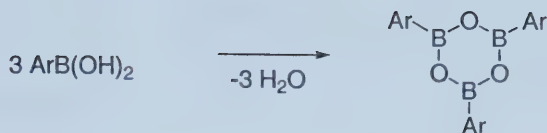
Scheme 10

Boronic acids have many other uses in organic chemistry. They have been used extensively in asymmetric synthesis as starting materials for Matteson's homologation reaction involving chiral boronates,²⁶ Corey's oxazaborolidines²⁷ and Yamamoto's chiral acyloxyborane Diels-Alder catalysts.²⁸ They have also been used for the ortho-specific α -hydroxyalkylation of phenols via aldehydes,²⁹ in palladium or nickel catalyzed protocols involving sulfonium salts,³⁰ thioesters,³¹ or thioalkynes,³² in nickel-catalyzed couplings with allylic compounds³³ and in electrophilic arylation with mercury (II) acetate/lead

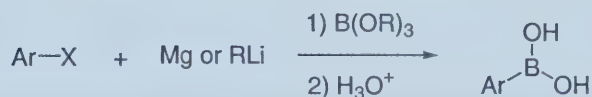
tetracetate.³⁴ There has also been several reports of oxidative *ipso*-substitution for the boronic group in arylboronic acids.³⁵

As one can see, from all the above uses, boronic acids are invaluable substrates to synthetic chemists. Therefore, there is a high demand for a diverse collection of commercial boronic acids. However, there are still relatively few boronic acids on the market,³⁶ and the ones available are quite simple. The scarcity of boronic acids can be explained by the absence of natural sources for these compounds and, more problematic, to the difficulty associated with the synthesis and derivatization of even the simplest functionalized ones.

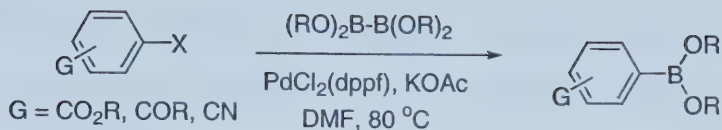
Most boronic acids undergo dehydration to form cyclic anhydrides (boroxines) and exist in either a dimer or a trimer form (Scheme 11). Because dehydration can occur at room temperature, it is difficult to obtain the acid without forming some amount of the corresponding anhydrides. This phenomenon causes analytical difficulties; melting points of boronic acids have minor value in characterization and purity assessments and elemental analyses of boronic acid derivatives are complicated by incombustible residues.³⁷ Commercial sources of boronic acids usually contain varying amounts of anhydrides.

**Scheme 11**

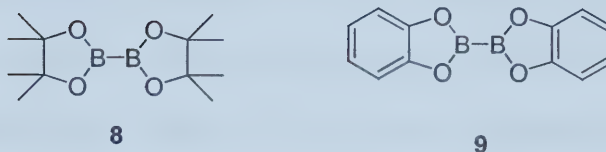
Classically, aryl boronic acids are synthesized from trialkylboronates and either Grignard or lithium reagents (Scheme 12).^{7a} These methods are efficient for making relatively simple boronic acids in large quantities.

**Scheme 12**

Recently, arylboronic esters have been directly obtained from arylhalides via the palladium catalyzed cross-coupling reaction of (alkoxy)diboron compounds³⁸ as illustrated in Scheme 13. This reaction tolerates various functional groups such as esters, nitriles and acyl groups. Compounds **8** and **9** are now commercially available for this process. However, although this method is extremely useful for making boronic esters, it does not result in the formation of free boronic acids and the cyclic esters are not always easily hydrolyzed to their corresponding boronic acids.



Scheme 13



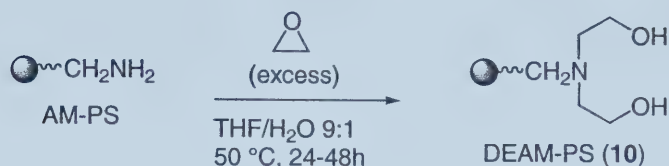
The amphiphilic properties of boronic acids make them difficult to isolate in solution. They are known to exist as water soluble tetrahedral boronate anions under basic conditions and are thought to be hydrated at neutral pH.³⁹ Organoboronic acids that contain other acidic or basic sites are extremely difficult to isolate especially using standard aqueous extractions. Boronic acids can often be purified by recrystallization. However, many boronic acids are not as easily purified using flash chromatography as very polar eluents are usually needed. When boronic acids are converted to their corresponding cyclic boronic esters, such as the robust pinacol esters, they can then usually be purified using silica gel chromatography.⁴⁰ However, this requires additional synthetic operations. The deprotection of the boronic ester after purification is often difficult and requires harsh conditions commonly resulting in incomplete reaction. Cleavage of the boronate ester can be done under hydrolytic conditions, reductively⁴¹ or with strong Lewis acids such as boron trichloride.⁴² These methods can be

destructive to fragile substrates and usually are only successful for simple hydrocarbon based boronic esters.⁴³ This deprotection problem is a limitation of the (alkoxy)diboron method mentioned in Scheme 13 for making boronic acids.

A general solid phase (SP) method for the immobilization, derivatization and purification of boronic acids would be complementary to the existing solution phase methods available. Solid phase organic synthesis (SPOS) is very useful because it can ease the isolation and purification steps that are almost always involved in solution phase synthesis. SPOS allows the use of excess reagents to drive the reaction to completion. The excess reagents and by-products can simply be filtered off at the end of the reaction while the substrate remains immobilized to the solid support. The SPOS of boronic acids would be especially useful in avoiding aqueous work-ups and other tedious isolation techniques such as flash chromatography or recrystallization.

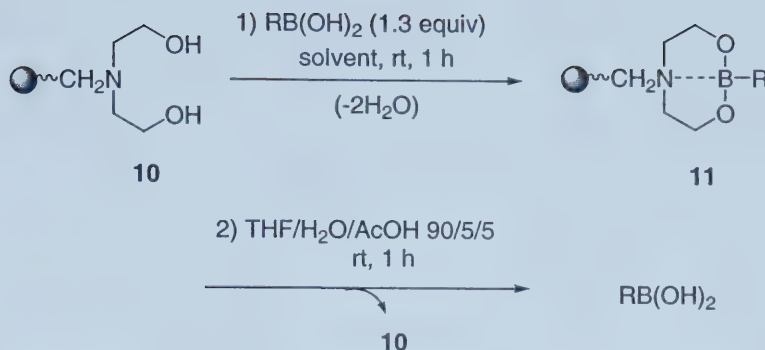
The Hall laboratory has recently reported the preparation of *N,N*-diethanolaminomethyl polystyrene (DEAM-PS) **10**, the first support capable of immobilizing, derivatizing and purifying boronic acids by their immobilization onto SP.⁴⁴ Other types of supports have also recently been described.^{45,46} However, unlike DEAM-PS, these supports either need harsh cleavage conditions to release the boronic acids from SP or they do not release the free boronic acid from SP at all, but instead do so by chemically altering the boronic acid in order to release modified substrates. DEAM-PS (**10**) was first synthesized from commercial aminomethyl polystyrene (AM-PS) via a double alkylation with ethylene oxide in a sealed, pressure-resistant tube (Scheme 14). The resulting

resin showed characteristics and a loading level that verified the clean and complete reaction of AM-PS to give DEAM-PS (**10**). Alternate syntheses of DEAM-PS (**10**) have since been reported.⁴⁷



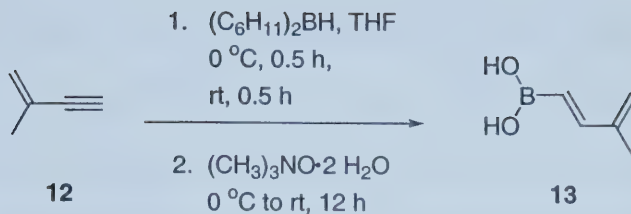
Scheme 14

DEAM-PS was found to be effective at immobilizing a variety of commercial electron-rich and electron-poor arylboronic acids via the formation of a stable boronate linkage between the resin and the boronic acid (Scheme 15). The putative coordination of the nitrogen lone pair to the empty *p* orbital on the boron acts as an additional stabilizing factor. The boronic acids were recovered intact after cleavage from the solid support using a THF/H₂O/AcOH (90/5/5) cleavage mixture. The development of the diethanolamine anchor was insightful because it takes advantage of the fact that diethanolamine boronate adducts have long been used to stabilize, purify, and characterize boronic acids.⁴⁸



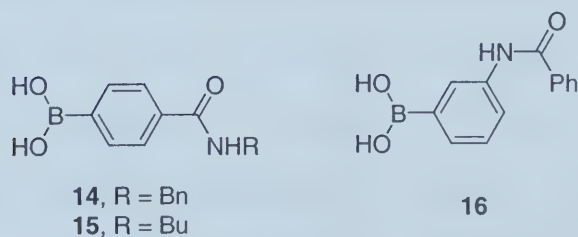
Scheme 15

DEAM-PS can also be used as a scavenger resin to isolate boronic acids synthesized in solution. Dienylboronic acid **13** can be prepared by the hydroboration of enyne **12** followed by oxidation with trimethylamine *N*-oxide (Scheme 16). Isolation and purification of the product **13** from by-products using traditional solution phase techniques is quite difficult and tedious. However, with DEAM-PS it can be selectively captured out of the complex reaction mixture. Once attached to DEAM-PS, the excess reagents and cyclohexanol by-products can be rinsed away. Subsequent release of the boronic acid from DEAM-PS resulted in pure boronic acid **13**.⁴⁴



Scheme 16

Preliminary studies in the Hall group with carboxylic acid and amine functionalized arylboronic acids supported onto DEAM-PS resin hinted that the resin could be useful for their derivatization. The DEAM-PS boronate linkage in **11** was resistant to standard carbodiimide methods for amide bond formation and subsequently successful for the synthesis of **14**, **15** and **16**.



In this thesis, a more extensive study on the properties of DEAM-PS **10** and the chemistries compatible with the DEAM-PS boronate linkage of **11** will be reported. The goal has been to determine the synthetic scope of DEAM-PS in order to realize its usefulness to derivatize functionalized boronic acids. This way, it could become an invaluable tool to organic chemists involved in organoboronic acid research.

DEAM-PS can also have applications in solid phase combinatorial chemistry. Combinatorial chemistry involves modern techniques that allow for the rapid synthesis of large libraries of small molecules often used in biological testing.^{49,50} The majority of libraries that have been synthesized utilize a linear strategy, consisting of functional group manipulations in a sequential fashion starting with one support-bound functionality. A limitation to this method is that the functionality and protecting groups introduced early in the synthesis must be stable to all further reaction conditions. This limitation could be overcome by using a convergent solid-phase approach for the construction of libraries. In this respect, resin-to-resin transfer reactions (RRTR) could be useful as tools for convergent SPOS. Convergent SPOS would make it possible to synthesize and store many libraries on different supports. These libraries could then be combined accordingly and quickly lead to new libraries of compounds. The decrease in the number of time-consuming cleavage and transfer operations using a convergent synthesis as compared to a linear one is especially advantageous when preparing large libraries via manual or automated means.

RRTR consists of two or more resin bound substrates where one resin bound substrate is transferred to solution and subsequently coupled to the other resin-bound substrate. RRTR are convergent because two or more fragments of a given molecule are synthesized on separate supports and then combined in the transfer step. A chaperone or neutral chemical agent is required to transfer one resin bound substrate to solution before it can couple to another resin-bound substrate. Because this chaperone molecule has to be compatible with the

reaction conditions, the development of RRTR is typically more challenging than comparable processes in solution phase.

RRTR were first reported in the 1970's. They were used as a tool for the mechanistic determination of several reactions such as acyl and phosphate transfer.⁵¹ It was not until recently that there has been an interest to develop RRTR for synthetic purposes. DeGrado and colleagues explored the use of oxime resin **17** for a resin-to-resin acyl transfer reactions (Figure 3).⁵¹ *N*-Hydroxysuccinimide, **19**, was used as the chaperone molecule liberating the acyl group from oxime resin support **18** to generate the active ester **20** in solution. The active ester **20** could then couple *in situ* with the amine resin **21** via an amide bond forming reaction. Products could then be released upon cleavage of resin **22**. DeGrado has also developed an aminoacyl RRTR, which involved the transfer of an aminoacyl group to a second amine resin via an isocyanate intermediate.⁵¹

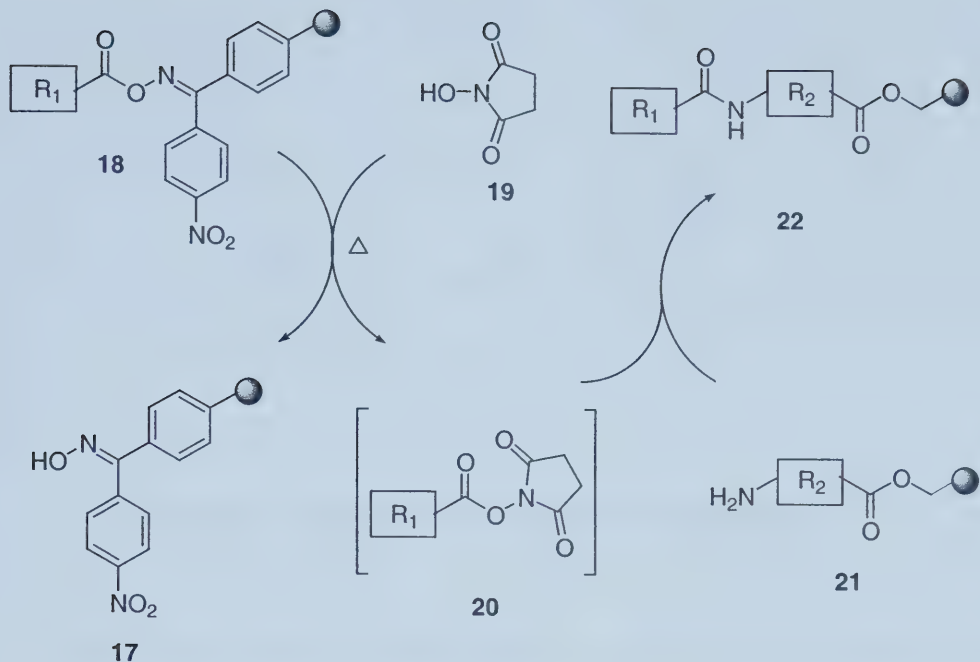


Figure 3. Resin-to-resin acyl transfer reaction

The Hall laboratory has reported the first RRTR for the formation of carbon-carbon bonds.⁵² A successful RRTR Suzuki coupling reaction was developed by coupling resin bound aryl iodides and arylboronic acids supported onto DEAM-PS **10** (Figure 4). Hydrolysis or transesterification on the DEAM-PS boronate linkage liberates the boronic acid or ester which is then transferred *in situ* to the haloarene resin in the presence of a base and a palladium(0) catalyst.

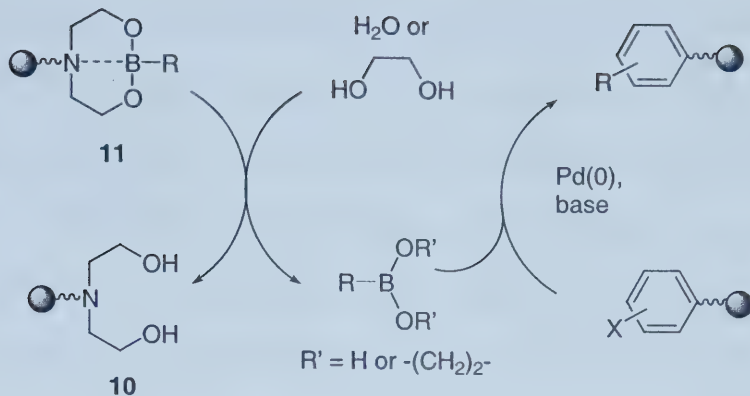


Figure 4. Resin-to-resin Suzuki coupling reaction

This RRTR works for both aqueous and non-aqueous Suzuki cross-coupling conditions. As well, boronic acids that were synthesized on DEAM-PS could be stored prior to their use in the transfer reaction. The usefulness of this new RRTR in combinatorial chemistry was demonstrated by the simple and practical production of a model library of unsymmetrical functionalized biphenyl compounds. Some of these compounds would have been difficult to access via a linear approach.⁵²

Another purpose of the research described in this thesis is to extend the scope of DEAM-PS to the development of a new RRTR. A strategy based on the Petasis borono-Mannich reaction (*vide supra*) will be investigated for the synthesis of arylglycine derivatives. Compounds of this nature are of particular interest for their biological activity.⁵³

Aside from the solid phase chemistry work with the DEAM-PS resin another focus of this work is to develop new reactions involving boronic acids by

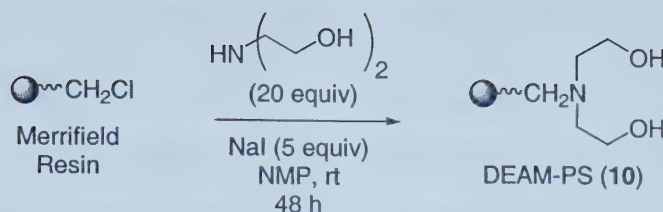
solution phase methods. Specifically, there is an interest to expand the scope of the Petasis borono-Mannich reaction. It would be useful to find methods to eliminate the requirement of the proximal hydroxyl group present in the carbonyl component (*vide supra*), a severe limitation of this reaction. Herein, several approaches that were investigated toward this goal are described.

In summary, the general objective of this thesis is to further evaluate the scope and potential of *N,N*-diethanolaminomethyl polystyrene (DEAM-PS) **10** for the immobilization, derivatization and RRTR of organoboronic acids. It is hoped that many more chemistries will be found that are compatible with the DEAM-PS resin, thereby making it a valuable tool to prepare novel boronic acids with ease and efficiency. It is also hoped that the scope of the Petasis borono-Mannich reaction will be expanded, in turn increasing the usefulness of boronic acids as substrates in organic synthesis.

II. Immobilization and Derivatization of Boronic Acids using DEAM-PS

A. Preparation of *N,N*-Diethanolaminomethyl Polystyrene (DEAM-PS) **10**.

A new route for making DEAM-PS (**10**) was developed for practical reasons by Michel Gravel in the Hall laboratory. This more convenient synthesis eliminated the need for a pressure-resistant tube that was used in the initial route with AM-PS and ethylene oxide as described in the introduction.⁴⁴ It was found that DEAM-PS **10** could easily be synthesized from commercial chloromethyl polystyrene resin, better known as the Merrifield resin (Scheme 17). Simple mixing of Merrifield resin, diethanolamine and sodium iodide at room temperature in NMP yielded DEAM-PS **10** after 48 hours. Resin **10** prepared by this easier, pressure-free method showed identical physical and spectroscopic characteristics as the resin prepared by the previous procedure. All the solid phase experiments regarding DEAM-PS presented in this thesis result from resin **10** that was synthesized using this latter method. Batches of resin **10** were typically made on a three-gram scale. This method will soon be applied for the commercial scale preparation of DEAM-PS.



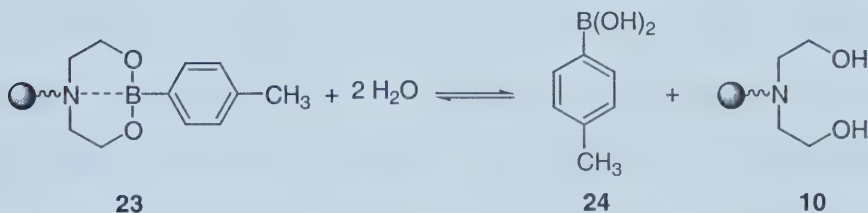
Scheme 17

B. Immobilization and Cleavage of Boronic Acids to and from DEAM-PS.

In the first account from the Hall laboratory, DEAM-PS was found to be effective at immobilizing a variety of boronic acids.⁴⁴ It was originally reported that a THF/H₂O/AcOH (90/5/5) cleaving mixture was effective for the release of boronic acids from DEAM-PS. It has since been found that no acid is necessary, thereby simplifying the protocol. Indeed, wet THF alone was sufficient to quickly release boronic acids from the resin. Typically, 5% volume/volume of distilled water in freshly distilled THF was used as the cleaving mixture. It was important that the THF was distilled over Na/benzophenone for the cleaving mixture even though water was added prior to its use. Distillation avoided contamination of products with 2,6-di-*tert*-butyl-*p*-cresol, a radical inhibitor added to commercial sources of THF to avoid. The cleaving mixture was only prepared as needed and never stored in order to avoid peroxide formation and therefore any subsequent oxidation of arylboronic acids during cleavage.

Next, the lability of the DEAM-PS boronate linkage **11** (shown on page 17) to water was examined. The effect of the amount of water on the immobilization

of boronic acids onto DEAM-PS **10** needed to be determined. In other words, how much water was needed to prevent immobilization and how fast did water cleave boronic acids from DEAM-PS? UV spectroscopy was used as a tool to answer these questions. Using DEAM-PS supported *p*-tolylboronic acid **23**, a UV spectroscopic assay was devised to quantitatively measure the amount of **24** hydrolyzed from the resin over a given period of time using varying amounts of water (Scheme 18). In theory, a minimum of two molar equivalents of water would be required to effect the quantitative cleavage of **24** from resin **23**.



Scheme 18

$$K_{\text{eq}} = \frac{[\mathbf{10}][\mathbf{24}]}{[\mathbf{23}][\text{H}_2\text{O}]^2}$$

To quantitatively measure the cleavage of **24** from DEAM-PS a calibration graph (concentration [mol/L] versus UV absorbance) was first constructed for boronic acid **24**. Then, known amounts of the supernatant were taken from a mixture of **23** in dry THF and a fixed amount of water. These aliquots were taken at different time intervals with both two and ten equivalents of water present. The

aliquots were diluted with THF before measuring their UV absorption. Concentrations of **24** below 1.3×10^{-4} M gave UV absorbance below 1.5. The UV readings were then compared to the calibration graph in order to determine the amount of **24** that had cleaved from DEAM-PS **10** at the time the specific aliquot was taken. Using this procedure, it was found that a greater amount of boronic acid was cleaved using ten equivalents of water over two equivalents although in neither case was the cleavage complete. Also, in both cases the extent of cleavage had reached a plateau after one minute indicating that by this time equilibrium had been reached. Thus, water damage to boronate linker **23** was not a result of how long it was in contact with water but rather a result of how much water it was exposed to. To determine the amount of water that was needed to quantitatively cleave boronic acid **24** from the resin, varying amounts of water (0-128 equivalents) were added to resin **23** swollen in THF. The percent cleavage of *p*-tolylboronic acid was then plotted against the amount of water added to DEAM-PS supported **23** as displayed in Figure 5. The data showed that a large excess of water, greater than thirty-two equivalents, was required to achieve full cleavage of boronic acid **24** from DEAM-PS **10**. Therefore, a 1 mL cleavage solution of 5% H₂O/THF (volume/volume) for 100 mg of resin (0.8-1.0 mmol g⁻¹ loading) was found to be sufficient to rapidly (~ one minute) and quantitatively release boronic acids from resin **10**. Although only one boronate linkage **11** was studied, we have found based on other experiences that 5% H₂O/THF is an efficient cleaving mix for a wide range of boronic acids.

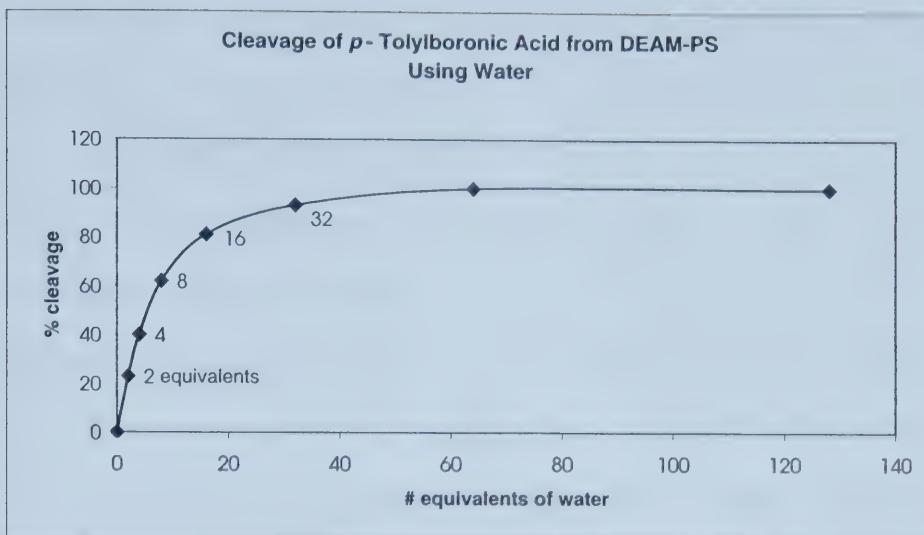


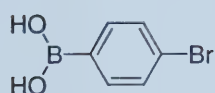
Figure 5. Cleavage of boronic acid 24 from DEAM-PS with water

Knowing that the hydrolysis was under equilibrium, one had to be concerned about how the formation of water would effect the boronic acid immobilization step. In principle, two molar equivalents of water are produced upon attachment of a boronic acid to DEAM-PS (10). According to Figure 5, the presence of two equivalents of water results in approximately 15-20% cleavage in THF. Therefore, immobilization can only proceed in about 80% yield in dry THF unless an excess of boronic acid is employed to shift the equilibrium. Alternatively, if the corresponding boroxines (*vide supra*) were used for attachment then only one equivalent of water would be released upon immobilization, leading to approximately 90% immobilization. Thus, immobilization in THF can have greater than 90% efficiency by using an excess of largely dehydrated boronic acid.

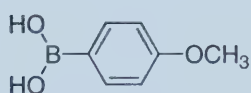
Next, the generality of boronic acid immobilization and cleavage on and off DEAM-PS was studied. These experiments were conducted by varying both the immobilization solvent, and the nature of the boronic acid (Table 1). The optimal conditions for immobilization previously discussed above for THF were used. DEAM-PS (**10**) was shaken with a slight excess (1.3 equivalents) of largely dehydrated boronic acids (pre-dried *in vacuo*) at room temperature for fifteen minutes. The percent yield of immobilization was based on the amount of boronic acid isolated after cleavage with 5% H₂O/THF. Boronic acid **24** was used as the model substrate for the solvent profile study. As revealed in entries 1-6, a wide range of anhydrous solvents could be employed, but the best immobilization result was obtained by using dichloromethane (entry 5). Presumably, because water is the least soluble in CH₂Cl₂, this solvent results in the least amount of cleavage and subsequently the greatest percent immobilization. Methanol gave the worst result, cleaving about 30% of **24** (entry 1). Although dichloromethane gave the best result, THF was typically used (entry 6) as the solvent of choice for immobilization as almost all boronic acids are soluble or at least partially soluble in THF, as compared to CH₂Cl₂. A series of arylboronic acids with different steric and electronic properties were studied to test the generality of the immobilization (entries 7-18). The immobilization was successful for both electron rich (entries 8, 13) and electron poor (entries 7, 9, 12) arylboronic acids. Boronic acids containing acidic (entry 9) and basic (entry 11) functionalities were also successful. Even the immobilization of alkenylboronic acid **36** was possible (entry 18). Attachment yields were high

except for *o*-carboxyphenylboronic acid **28** (entry 10), the exceptionally hindered **33** (entry 15), and the extremely electron poor **34** (entry 16). All the boronic acids were recovered pure and their appearance and characterization were in accordance with that of their initial state from commercial sources.

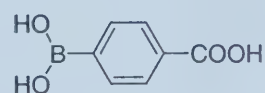
Table 1. Immobilization of various boronic acids onto DEAM-PS.^a



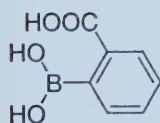
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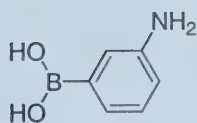
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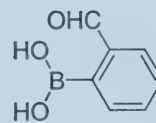
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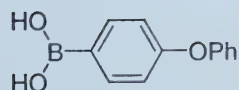
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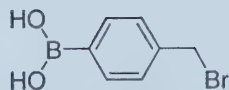
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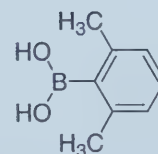
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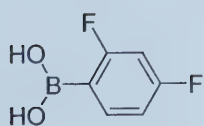
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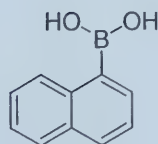
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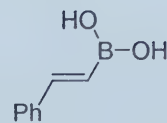
33



34



35



36

entry 1	boronic acid	solvent	yield (%) ^b	purity ^c
1	24	MeOH	72	> 95
2	24	NMP	80	> 95
3	24	Et ₂ O	90	> 95
4	24	Toluene	88	> 95
5	24	CH ₂ Cl ₂	98	> 95
6	24	THF	89	> 95
7	25	THF	97	> 95
8	26	THF	87	> 95
9	27	THF	90	> 95
10	28	THF	51	> 95
11	29	THF	91	> 95
12	30	THF	98 ^d	> 95
13	31	THF	93	> 95
14	32	THF	85	> 95
15	33	THF	46	> 95
16	34	THF	46	> 95
17	35	THF	89 ^d	> 95
18	36	THF	81	> 95

^a Coupling reactions were conducted by shaking resin **10** (1 equiv, 120 mg, 1.15 mmol/g) with the boronic acid (1.3 equiv) in the indicated solvent (1.5 mL) at rt for 1 hour in a polypropylene fritted vessel. ^b Yields of boronic acid recovered after cleavage from the resin with 5% water/THF for 1 min at rt and washing with 5% water/THF (3×). The resin was rinsed with the reaction solvent (3×) prior to cleavage. For entries 4 and 5, additional THF rinses were carried out (3×). The reported yields are an average of mass balance and internal standardization (see Experimentals for details) based on the loading of resin **10** measured by elemental analysis. ^c Estimated by comparison of ¹H NMR spectra of starting and recovered boronic acids. ^d Calculated only from mass balance, tendency of this boronic acid to form anhydrides made NMR spectroscopy quantification difficult.

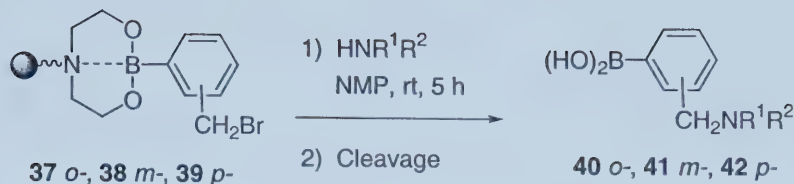
C. DEAM-PS for the Solid Phase Derivatization of Functionalized Boronic Acids.

One of the major goals of this work was to demonstrate the usefulness of DEAM-PS (**10**) for synthesizing novel arylboronic acids. To this end, it was necessary to show the compatibility of the DEAM-PS boronate linker **11** to different classes of standard transformations. It was realized from the results in previous section, that it would be favorable to employ anhydrous and alcohol free reaction conditions to avoid premature cleavage of boronic acid from DEAM-PS. Commercially available, functionalized arylboronic acids were immobilized onto resin **10** in high yields as described previously. Boronic acid products were cleaved with 5% H₂O/THF and in most cases there was no need for further purification. The newly derivatized arylboronic acids were characterized by ¹H NMR, ¹³C NMR, ES-MS and IR spectroscopies. The overall yields for the derivatized boronic acids include the yield of the initial boronic acid immobilization step, which was not quantitative as shown in the previous section even though a slight excess of boronic acid was used for immobilization. However, for simplicity all the starting boronic acids were not dried under vacuum prior to their attachment to DEAM-PS. Percent yields were usually calculated as an average between mass balance and internal standardization by ¹H NMR spectroscopy compared to the theoretical loading of resin **10** (see Experimental Section for details). These two methods generally gave results within 5% of one another.

i) Development of Reactions Compatible with DEAM-PS by Other Hall Group Members.

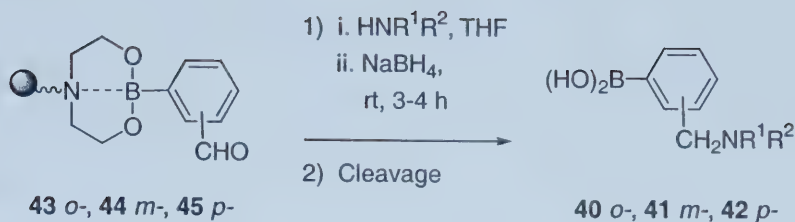
It was discovered either concurrently or previously to this work that the following types of chemistries were compatible with DEAM-PS: nucleophilic substitution, reductive amination and amide bond formation, which are briefly discussed below.

Mark Zak showed that DEAM-PS supported bromomethyl derivatized benzeneboronic acids could be displaced with both primary and secondary amines (Scheme19). The substitution reactions were efficient for both *meta* and *para* substrates **38** and **39**, but were unsuccessful for *ortho* cases giving mainly premature cleavage of products. However, the products that would have been achieved from *ortho* substrate **37** are obtainable from reductive amination chemistry (*vide infra*). The optimized reaction conditions were general to both the *meta* and *para* substrates, although different reaction conditions were needed with respect to the use of primary amines versus secondary ones. When secondary amines were employed, simply stirring **38** or **39** with 10 equivalents of the amine in NMP for five hours at room temperature resulted in good yield and purity of the desired product. In the case of primary amines, 50 equivalents of the amine and the use of low loading resin were required to avoid cross-linking by double alkylation.



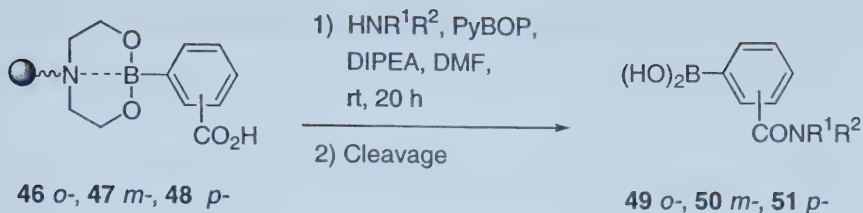
Scheme 19

Mark also discovered optimal conditions for the reductive amination on DEAM-PS supported formyl-substituted benzeneboronic acids (Scheme 20). It was necessary to pre-form the imine and then reduce it with sodium borohydride. Only the *ortho* substrate **43** resulted in the desired products in satisfactory yield and good purity. Both *meta* and *para* substrates **44** and **45** afforded impure products. The use of secondary amines as substrates in the reductive amination reaction was later studied by myself but was met with little success, no sign of the desired products were detected by ES-MS or ^1H NMR spectroscopy. Although this chemistry was only successful for the *ortho* substrates, it complements the results from the nucleophilic displacement of alkyl bromides which only worked with the *meta* and *para* substituted compounds (*vide supra*). The reductive amination and nucleophilic substitution chemistries ultimately lead to the same products and therefore all aromatic substitution products (*ortho*, *meta*, and *para*) were synthetically available.



Scheme 20

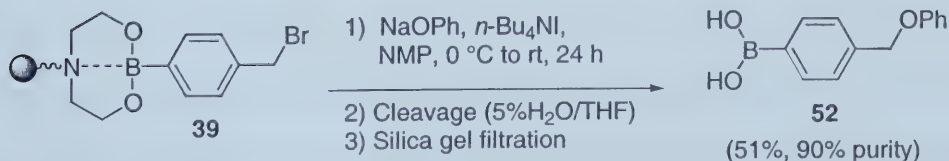
Chris Bérubé and Michel Gravel worked on the amide bond forming reaction shown in Scheme 21. Both *meta* and *para* substrates **47** and **48** were successful but the *ortho* substrate **46** failed. Simple stirring of carboxylic acid **47** or **48** with an amine, PyBOP and DIPEA in DMF at room temperature for 20 hours resulted in good yields of the desired products. A noteworthy case that illustrates the usefulness of DEAM-PS in making boronic acid derivatives is the synthesis of boronic acid **51** ($\text{R}^1, \text{R}^2 = \text{H}, (\text{CH}_2)_2\text{NEt}_2$). This boronic acid is a known melanoma seeking agent with potential use in BNCT.⁵⁴ The reported solution phase synthesis of this boronic acid was much more involved and required protection of the boronic acid.⁵⁴



Scheme 21

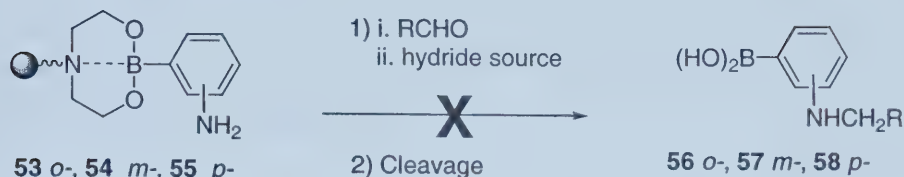
ii) Nucleophilic Substitution with an Oxygen-Based Nucleophile.

Sodium phenoxide was investigated as an example of an oxygen-based nucleophile for the substitution reaction (Scheme 22). A series of trials revealed that the reaction worked equally well in NMP or DMF and only a slight excess of PhONa was needed. The integration in the ^1H NMR spectrum of crude product **52** was not correct in the aromatic region. The ^1H NMR spectrum cleaned up nicely after filtration of crude **52** through a silica gel plug using 10% MeOH/ CH_2Cl_2 as an eluent. This reaction only proceeded to give a moderate yield of **52** and it was suspected that the reactive phenoxide ion caused substantial premature cleavage from DEAM-PS.



Scheme 22

iii) Reductive Amination of Anilines (Scheme 23).

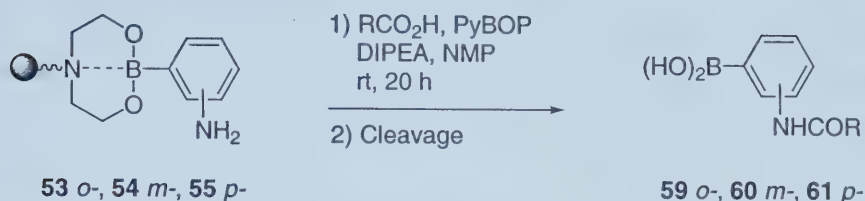


Scheme 23

The reductive amination of supported anilines yielded poor results with substrate **54** as discovered by colleague Mark Zak. The same general procedure was used as for the formyl-substituted boronic acids mentioned above. Several reaction conditions and two different aldehydes (benzaldehyde and butyraldehyde) were tried but in all cases the reductions either did not go to completion or failed completely for unknown reasons. Perhaps, the supported anilines are not nucleophilic enough as compared to aliphatic amines. Later, the same procedure was applied to the *ortho* substrate **53**, and benzaldehyde by myself. *Ortho*-aminophenylboronic acid was obtained from the reduction of *ortho*-nitro-phenylboronic acid with hydrogen and palladium on carbon at 60 psi according to a literature procedure.⁵⁵ Although the reductive amination had worked for the *ortho* substrate in the inverse reaction (*vide supra*) only a small yield of impure material was obtained after cleavage from the solid support in this case. Next, addition of $\text{Ti}(\text{O}i\text{-Pr})_4$ was tried in order to activate the benzaldehyde toward imine formation before subsequent reduction by NaBH_4 , but unfortunately a low yield of a slightly cleaner product was obtained. Based on these findings, it

appeared that the reductive amination of anilines was not compatible with the DEAM-PS boronate linkage.

iv) Anilide Formation (Scheme 24).



Scheme 24

As carbonyl-containing compounds are an important class of molecules, methods for their synthesis were further investigated. Anilide formation (Scheme 24), the inverse to the amide bond forming reaction illustrated in Scheme 21, was also found possible. The Hall group had previously synthesized anilide-derivatized boronic acids **60** from the reaction of aniline **54** with acid chlorides.⁴⁴ This reaction worked for aromatic acid chlorides but was not general and failed for aliphatic ones. However, it has since been discovered that it is more effective to couple carboxylic acids to supported anilines. As shown in Table 2, all substitution patterns (*o*, *m*, *p*) were successful for this chemistry giving 50-80% yields. *Para*-aminophenylboronic acid was obtained from *para*-nitrophenylboronic acid by the same general method used to access *ortho*-aminophenylboronic acid (*vide supra*).⁵⁵ PyBOP was found to be the coupling

reagent of choice, giving substantially higher yields than a DIC/HOBt protocol.⁵⁶

The reaction is very general with regards to the carboxylic acid used. Aromatic, aliphatic, alkenyl, and alkynyl carboxylic acid derivatives were all successful as well as an amino acid: Fmoc-protected alanine (entry 7).

Table 2. Anilide synthesis from anilines 53-55.^a

entry	substrate	product ^a {R}	yield ^b (%)	purity ^c (%)
1	53	59a {CH ₂ CH ₃ }	61	> 95
2	53	59b {Ph}	60	> 90
3	54	60a {CH ₂ CH ₃ }	72	95
4	54	60b {Ph}	82	95
5	54	60c {CH ₂ CH ₂ CH=CH ₂ }	70	> 95
6	54	60d {C≡CPh}	75	> 95
7	54	60e {(S)-CH(Me)NHFmoc}	51	95
8	55	61a {CH ₂ CH ₃ }	61	> 95
9	55	61b {Ph}	46	95

^a Typical scale 0.1 mmol. Reactions were carried out by shaking the supported aniline with the carboxylic acid (2 equiv), PyBOP (2 equiv), DIPEA (4 equiv) in NMP at rt for 20 h. ^b Non optimized yields of crude products after cleavage from the resin with 5% H₂O/THF and drying *in vacuo* for > 12 hours. The reported values are usually an average of mass balance and internal standardization (see Experimental Section for details). ^c Estimated from ¹H and ¹³C NMR spectroscopic data.

Although all the *meta* and *para* substrates **54** and **55** gave the expected products the exact nature of the *ortho* products was not certain at first. *Ortho*-substituted boronic acid products **59a** and **59b** were found extremely insoluble in all common organic solvents. The minimal solubility of these *ortho* products in methanol allowed one to obtain ¹H NMR spectra of these compounds but not ¹³C NMR spectra, which typically require a higher concentration. An ES-MS analysis

on the *ortho* products showed base peaks corresponding to the loss of water from the expected products **59**. *Ortho* substituted anilides **59** most likely exist in a cyclic monodehydrated form (**B** in Figure 6), which has already been reported in the literature when $X = \text{Me}$ and $R = \text{H}$.⁵⁵ It has also been proposed in the literature that weakly nucleophilic species such as water or methanol can add in a 1,4-fashion to compounds like heterocycle **B** (see **B**→**C** in Figure 6), which was supported by a multisolvent ^{11}B NMR spectral study.⁵⁵ Trigonal-planar substituted, sp^2 hybridized neutral boron atoms such as in **B** and tetrahedral substituted, sp^3 hybridized anionic borate centers such as in **C** are easily distinguished by chemical shifts. The difference in the physical properties of the *ortho* products **59** (i.e. solubility) from that of the *meta* and *para* products **60** and **61** are probably attributed to the equilibrium process shown in Figure 6.

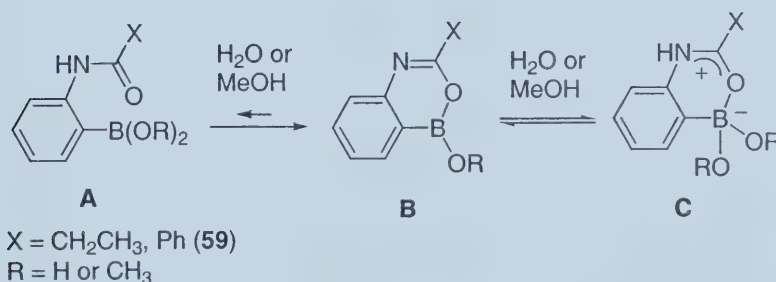
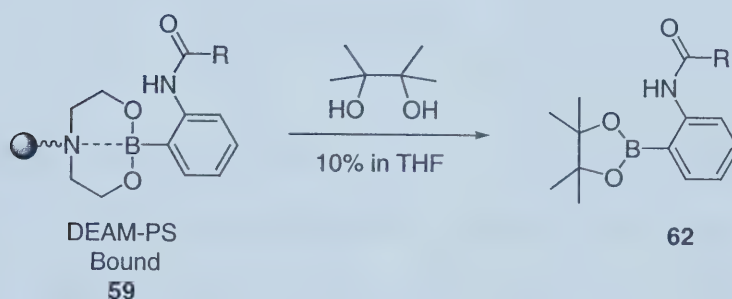


Figure 6. Possible equilibrium process of an *ortho*-acylamino boronic acid derivative

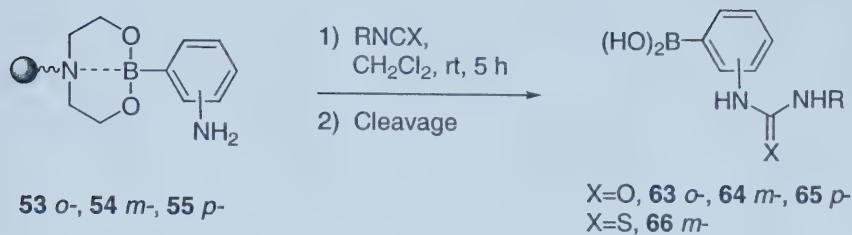
To fully characterize the *ortho*-boronic acids **59** their corresponding pinacol esters **62** were prepared. This esterification was accomplished by

cleaving the products from solid phase with 10% pinacol/THF followed by purification using silica gel column chromatography (Scheme 25). It was not possible to make pinacol esters **62** once the boronic acids **59** had already been cleaved from DEAM-PS with 5% H₂O/THF. This failure was either because of solubility issues with **59** or the existence of boron heterocycles such as **B** and **C** shown above in Figure 6.



Scheme 25

v) Urea and Thiourea Formation (Scheme 26).



Scheme 26

The synthesis of both *meta* and *para* substituted ureas **64** and **65** (Scheme 26) were very straightforward on DEAM-PS and these results are displayed in Table 3.⁵⁷ Simple mixing of **54** or **55** with various arylisocyanates in dichloromethane for 5 hours at room temperature resulted in excellent yields ($\geq 80\%$) of either **64** or **65**. Aliphatic isocyanates needed longer reaction times and resulted in slightly lower yields (entries 1, 6). The reaction worked well for both electron rich (entries 3, 8) and electron poor (entries 4, 9) arylisocyanates. Thiourea derivative **66** could also be made using the same protocol (entry 5). Although the *ortho* substrates **53** did yield the desired products **62**, they were contaminated with substantial amounts of double addition products. Unfortunately, the formation of these undesired products was unavoidable even after trying different reaction times and using the minimal single equivalent of the isocyanate reagent.

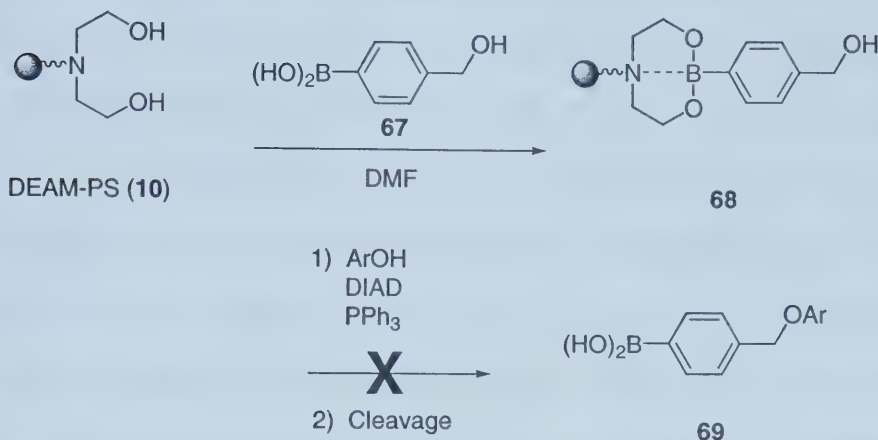
Table 3. Synthesis of ureas and thiourea from anilines 54 and 55.

entry	substrate	conditions ^a	product {R}	yield ^b (%)	purity ^c (%)
1	54	B	64a {CH(CH ₃) ₂ }	71	95
2	54	A	64b {Ph}	79	> 95
3	54	A	64c {4-MeO-C ₆ H ₄ }	82	> 95
4	54	A	64d {4-NO ₂ -C ₆ H ₄ }	80	> 95
5 ^d	54	A	66 {Ph}	85	95
6	55	B	65a {CH(CH ₃) ₂ }	65	> 95
7	55	A	65b {Ph}	85	> 95
8	55	A	65c {4-MeO-C ₆ H ₄ }	88	> 95
9	55	A	65d {4-NO ₂ -C ₆ H ₄ }	92	95

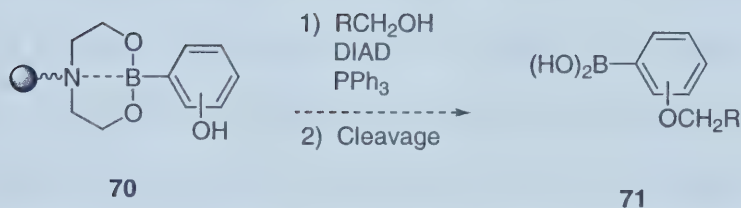
^a Typical scale 0.1 mmol. A: Reactions were carried out by shaking the supported aniline with the isocyanate (2 equiv), in CH₂Cl₂ at rt for 5-6 h. B: longer reaction time (20-45 h). ^b Non optimized yields of crude products after cleavage from the resin with 5% H₂O/THF and drying *in vacuo* for over 12 hours. The reported values are usually an average of mass balance and internal standardization (see Experimental Section for details). ^c Estimated from ¹H and ¹³C NMR spectroscopic data. ^d Isothiocyanate was used in place of isocyanate.

vi) Mitsunobu Reaction with Phenol Derivatives (Scheme 27).

eq. 3)



eq. 4)



Scheme 27

We also examined the application of the Mitsunobu reaction⁵⁸ to make boronic acid/aryl ether derivatives on DEAM-PS (Scheme 27). Either the alcohol or the nucleophile (phenols in our case) could have been anchored to solid support (equation 3 versus 4). The boronic acids needed to make **70** were neither commercially available nor easily synthesized. Thus, commercial 4-(hydroxymethyl)phenylboronic acid **67** was attached to DEAM-PS (**10**) and the

reaction in equation 3 was explored. Boronic acid **67** was very insoluble in common organic solvents and did not immobilize to DEAM-PS even when THF was used as the reaction solvent. One had to use either DMF or NMP as the immobilization solvent for this particular organoboronic acid. Unfortunately, under no circumstances did the Mitsunobu reaction work on the primary alcohol of DEAM-PS supported **67**. Both unsubstituted phenol or *p*-cresol were used and both DIAD and DEAD were tried to activate the triphenylphosphine. Varying reagent ratios, order of reagent addition, reaction concentration, reaction time (16-72 h) and solvents (THF and NMM) were tried. Each time, starting boronic acid **67**, what appeared to be trace amounts of product by ^1H NMR and unidentified products relating to either DIAD or DEAD were obtained. It was believed that if there were empty sites on DEAM-PS still present after the attachment of boronic acid **67**, then perhaps the free alcohol functionality of the DEAM-PS diethanolamine arms could interfere with the Mitsunobu reaction. With these results, it appears that the Mitsunobu reaction is not compatible with the DEAM-PS boronate linkage. However, products of type **67** are still available via the nucleophilic substitution reaction shown in Scheme 22.

vii) The Ugi Reaction

The four-component Ugi reaction (U-4CR) was discovered in 1959 for making peptide-like molecules (Figure 7).⁵⁹ The four components of this condensation reaction consist of an acid, an amine, a ketone or aldehyde and a

C-isocyanide. A simplified mechanism of the U-4CR is shown in Figure 7. In the first step, there is the formation of an imine, which then behaves as a base towards the acid component to provide an iminium intermediate. The isocyanide adds to the iminium followed by attack of the acid on the carbon of the isocyanide. The Ugi product is then obtained after an intramolecular acylation reaction followed by the rearrangement of a hydroxylamine to an amide. There are no commercial arylboronic acids that contain an isocyanate function, thus attaching an arylboronic acids which contained the amine, aldehyde, or acid component to DEAM-PS was focused on.

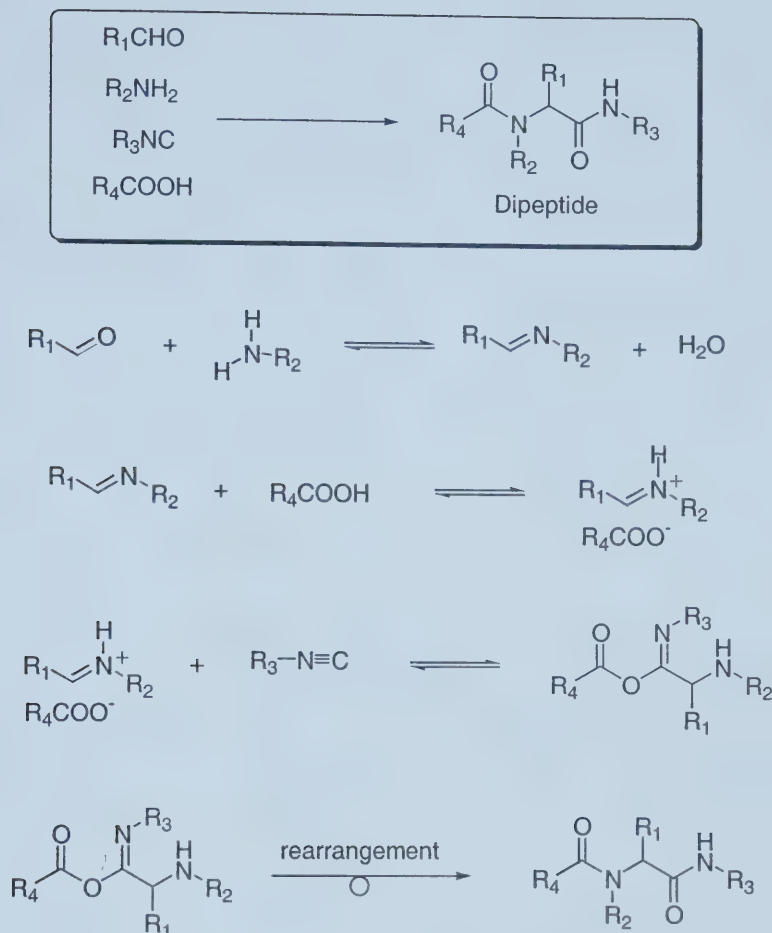
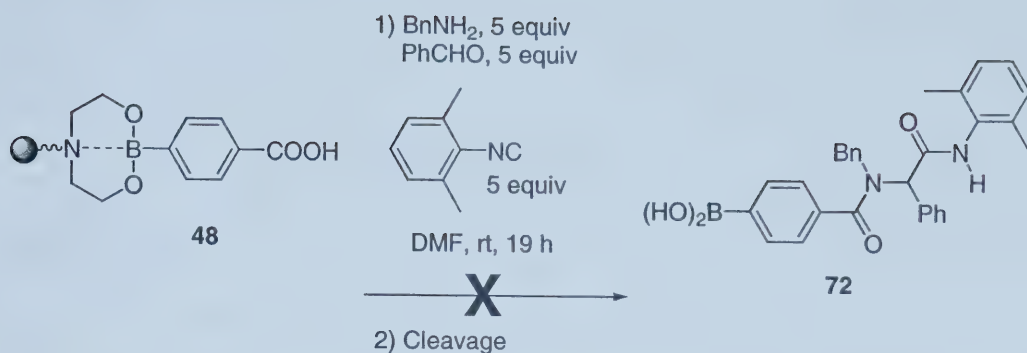


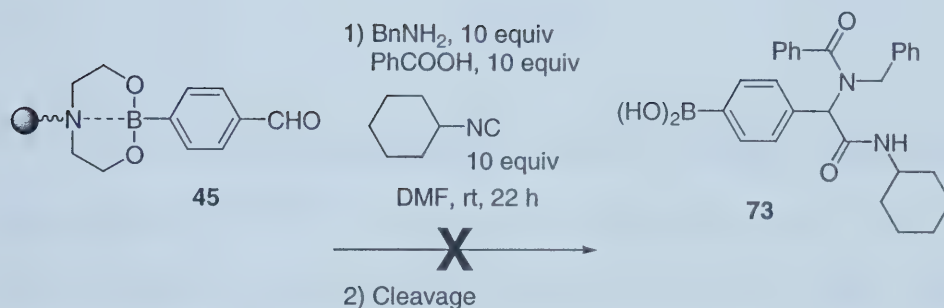
Figure 7. Summary of the U-4CR Mechanistic Pathway

Initially, either the acid or aldehyde component was anchored to DEAM-PS (equation 5 and 6 in Scheme 28) but in neither case were the desired products **72** and **73** obtained. The cleaved product of equation 5 showed no sign of the methyl groups from the isocyanide by ^1H NMR spectroscopy. The reaction in equation 6 resulted in the presence of a *para*-substituted aromatic compound that did not correspond to cleaved starting material.

eq. 5)



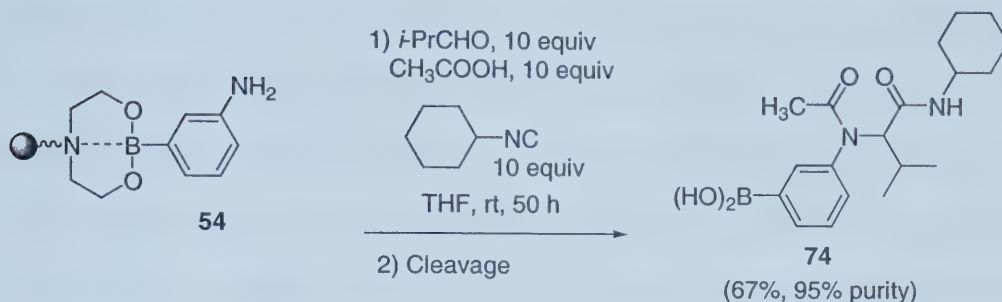
eq. 6



Scheme 28

In light of these results, the amine component was anchored to the resin. *Meta*-aminophenylboronic acid was used as the model amine as it is the only isomer commercially available. In this case, we initially verified the solution phase U-4CR with unsubstituted aniline as the amine component. We used these results as a starting point for initial reaction conditions to apply to solid phase. Eventually, after several trials with different reaction times and ratios of

reagent, suitable conditions were found for a successful U-4CR using a DEAM-PS supported boronic acid (Scheme 29).



Scheme 29

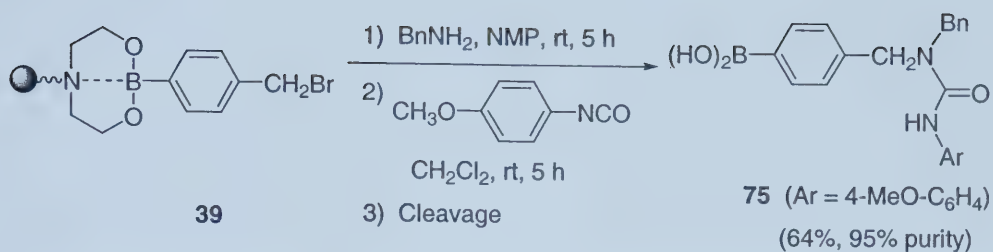
Next, the optimized conditions for the supported *meta* substituted aminophenylboronic acid **54** were applied to the *ortho* case. The ¹H NMR spectrum revealed an impure product that was obtained in low yield (< 40%). No optimization studies on this substrate were done. Although the generality of the solid phase U-4CR on DEAM-PS was not studied, it has been shown that the diethanolamine boronate linkage could tolerate this elaborate transformation.

viii) Multi-Step Transformations

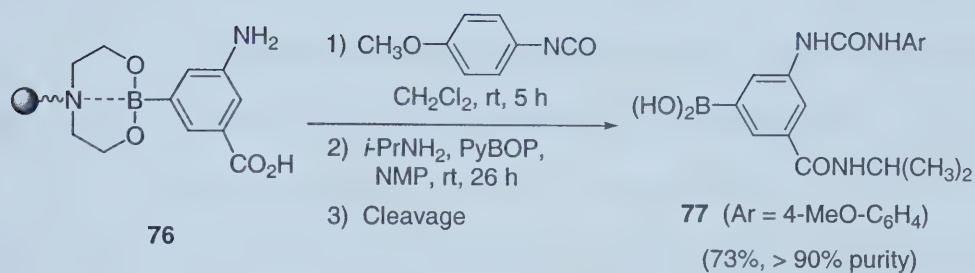
A few examples of sequential reactions were explored in order to determine whether DEAM-PS bound boronic acids could withstand more than one reaction on solid support (Scheme 30). Product **75** was obtained after

nucleophilic substitution of alkyl bromide **39** with benzylamine followed by urea formation with *p*-methoxyphenylisocyanate (equation 7). This two step sequence resulted in a 64% yield and good purity of compound **75** after cleavage from DEAM-PS. Bifunctional boronic acid **76** was also derivatized (equations 8 and 9). The amine function of **76** could first be converted to a urea and then the carboxylic acid portion of **76** could be converted to the isopropyl amide (equation 8). This two-step reaction gave product **77** in a 73% yield and in greater than 90% purity. In addition, the carboxylic acid of **76** could first be converted to an amide, followed by a U-4CR with the leftover amine moiety to give **78** in good purity and somewhat lower yield after cleavage from the solid support (equation 9). These examples show that multi-step reactions can be carried out on the DEAM-PS resin although anhydrous reaction conditions must be used in each step in order to minimize premature release of the supported boronic acids. The yields of each individual transformation dictate the number of sequential reactions that can be performed on resin **10** and still result in a satisfactory amount of desired product.

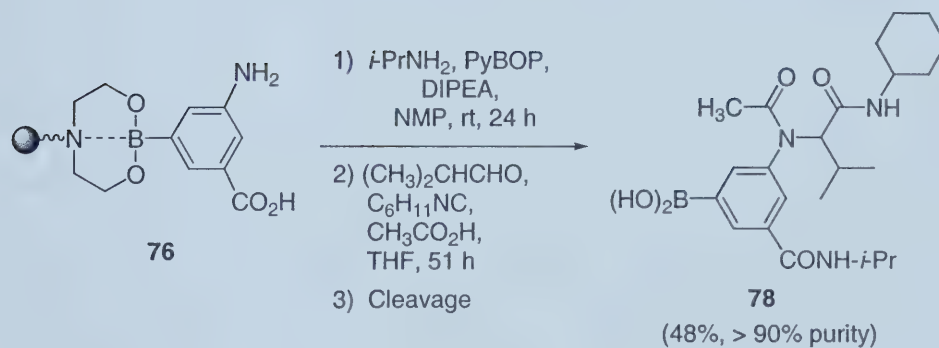
eq. 7)



eq. 8)



eq. 9)



Scheme 30

III. Application of DEAM-PS in a Resin-to-Resin Transfer Reaction

To further extend the utility of the DEAM-PS resin, its use in a resin-to-resin transfer reaction was examined. This RRTR was based on the borono-Mannich reaction for the preparation of new arylglycine derivatives. RRTR systems allow for the convergent solid phase synthesis of molecules that can often be difficult to access via a linear solid phase strategy, while their practical aspects show promise toward high-throughput combinatorial library synthesis. The general approach is outlined in Figure 8. As described in section II (part B), it was known that the DEAM-PS boronate adducts **11** could be cleaved under mild conditions, such as exposure to alcohols.⁵² Conveniently, alcohols are also compatible solvents for the borono-Mannich reaction. It was envisioned that an alcohol could act as the chaperone molecule and transfer the boronic acid from the DEAM-PS resin into solution as the corresponding boronic ester. The thus-formed boronic ester could then couple *in situ* to a resin bound imine **81** formed between amine functionalized resin **79** and the required activated aldehyde **80**, glyoxylic acid. Transfer of the R-group from the boron to the resin bound iminium species **81** would lead to the formation of supported product **82**. Subsequent cleavage of **82** would release the desired glycine derivative.

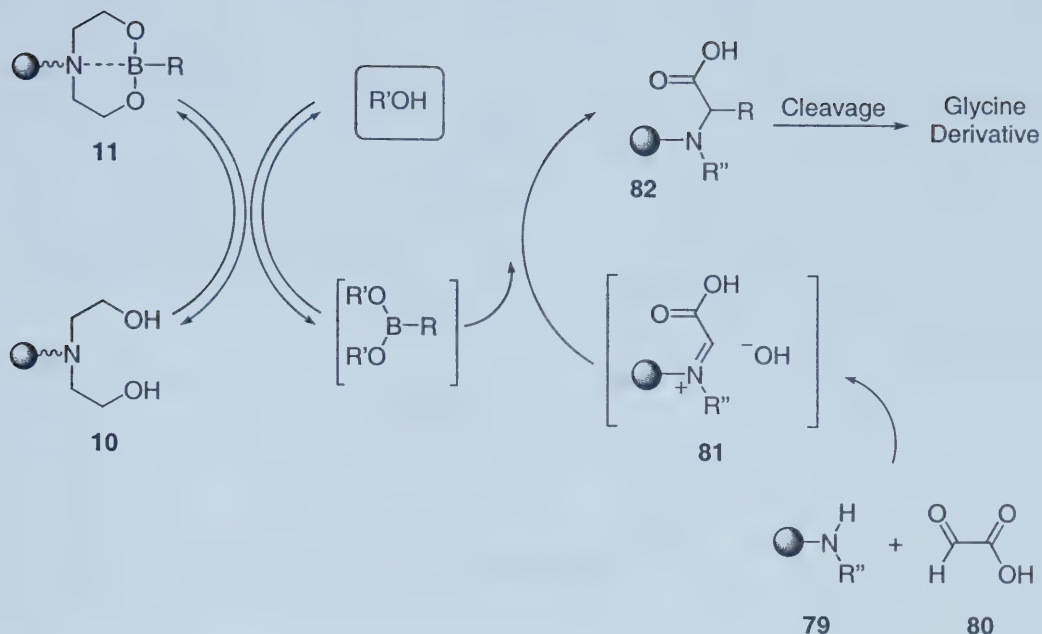
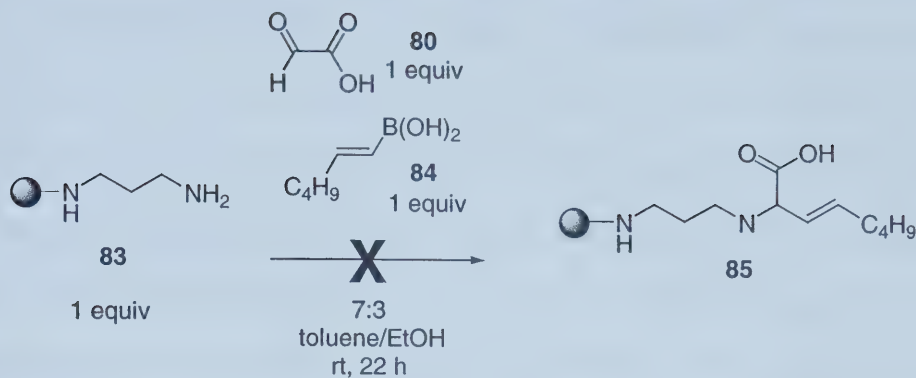


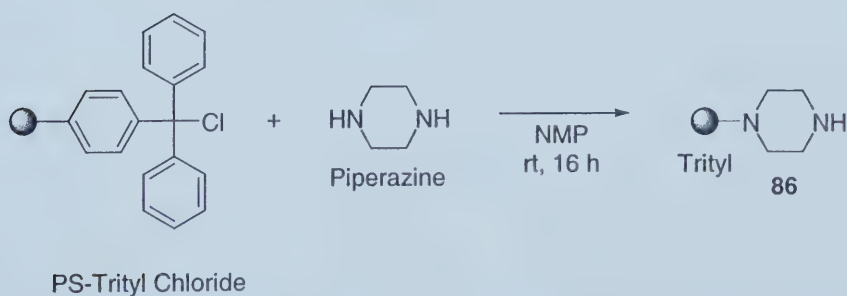
Figure 8. Resin-to-resin borono-Mannich reaction

At the onset of this project, it needed to be determined if the borono-Mannich reaction could be applied to solid phase before a resin-to-resin protocol could be developed. Initial studies used boronic acid **84**, glyoxylic acid **80** and 1,3-diaminopropane trityl resin **83** as the solid supported amine (Scheme 31). Reported reaction conditions were mimicked as closely as possible after their reproducibility in solution had been verified.^{11a} Unfortunately, the desired product could not be detected by 1H NMR spectroscopy or ES-MS after cleavage of the solid support. Only the trifluoroacetic acid (TFA) salt of 1,3-diaminopropane was obtained after cleavage with 5% TFA/ CH_2Cl_2 . These results indicated that primary amines are probably not suitable for the solid phase borono-Mannich reaction.



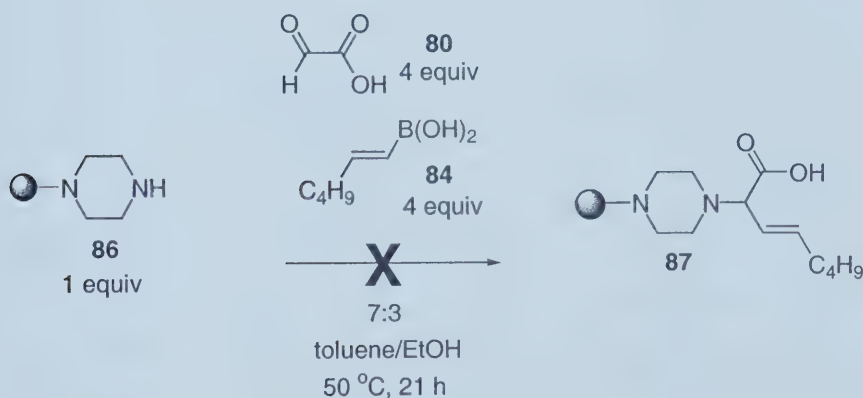
Scheme 31

Therefore, the focus was changed to the use of resin-bound secondary amines. Piperazine trityl resin **86** was used as the model secondary amine. This resin was synthesized by stirring trityl chloride resin with an excess of piperazine in NMP at room temperature for 16 hours (Scheme 32).



Scheme 32

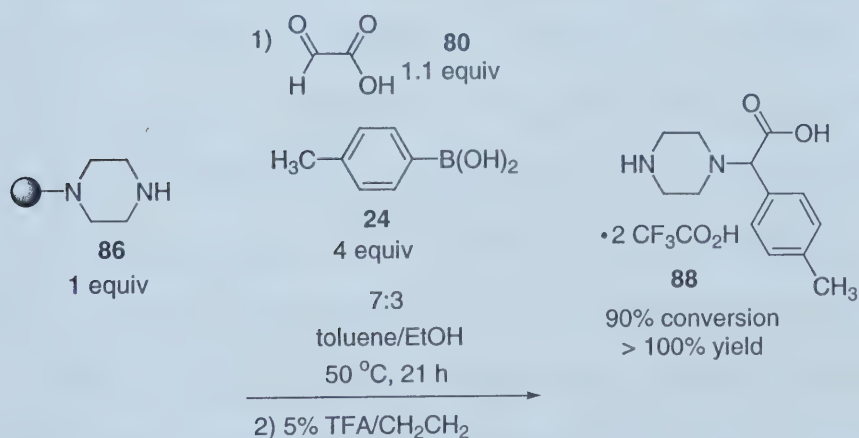
With resin **86** in hand, solid phase secondary amines were ready to be tested towards the borono-Mannich reaction. One equivalent of amine resin **86** was mixed with four equivalents of both boronic acid **84** and glyoxylic acid (Scheme 33). The experiment was run at 50 °C because secondary amines often required heating in solution phase literature examples.^{11a} A trace yield of crude material was obtained after cleavage from the solid support, and the desired product (cleaved **87**) was observed by ES-MS. It was later discovered, through control experiments, that the excess glyoxylic acid was inducing cleavage of piperazine and its derivatives from trityl resin.



Scheme 33

Therefore, the reaction conditions were modified by using only a slight excess of glyoxylic acid. It was suspected that product **87** may have been sensitive to the TFA used in the cleavage mix so a new model boronic acid, *p*-tolylboronic acid **24**, was employed. This time, a successful reaction was

observed with the formation of the bis(trifluoroacetate) salt **88** (Scheme 34). Unfortunately, the reaction only proceeded with 90% conversion, a concern to keep in mind. An excess of glyoxylic acid was also tried in the presence of a DIPEA buffer to avoid premature cleavage of product and push the reaction to completion. The results of these experiments, however, were no better than just using 1.1 equivalents of glyoxylic acid. Later, it was determined that product **87** was not sensitive to TFA but *p*-tolylboronic acid **24** was continued to be used as the model boronic acid. Now that it was determined that the borono-Mannich reaction was applicable to solid phase, the next step was to apply this process to a resin-to-resin transfer strategy.



Scheme 34

At the resin-to-resin optimization stage, resin bound *p*-tolylboronic acid **23**, piperazinetrityl resin **86**, and glyoxylic acid monohydrate **80** were used to determine reaction conditions. The reaction was rather slow and strongly

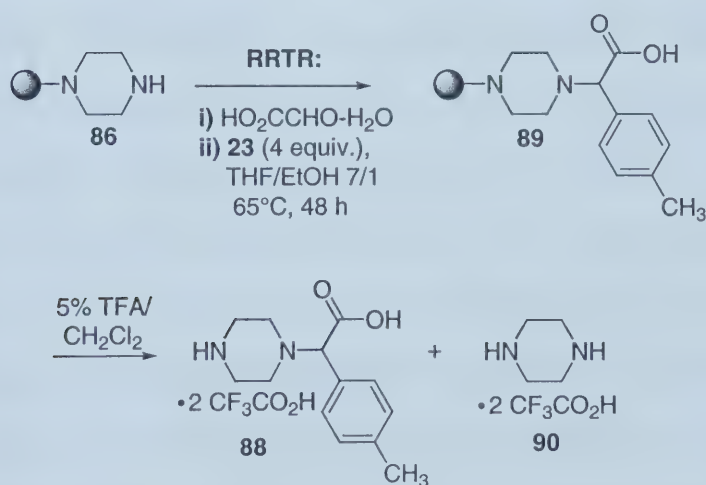
dependent on the nature of the solvent system (Table 4). The reaction worked best at 65 °C when a 7/1 mixture of THF/EtOH was used as the solvent system (entry 5). It was originally thought that higher boiling solvent mixtures such as DMF/*n*-BuOH or dioxane/*n*-BuOH would have been able to push the reaction to completion. However, results with these solvents at 95 °C were not as good as those with THF/EtOH at 65 °C. It was also found that the use of a semi-automated synthesizer generally gave better results for the RRTR than performing the reactions in silanized round bottom flasks. The current optimal conditions are displayed in Scheme 35. Piperazinetrityl resin **86** (1 equivalent) and glyoxylic acid monohydrate (1.1 equivalent) were first mixed in THF at room temperature for two hours to pre-form the imine rather than adding all the reagents at once. Then, four equivalents of DEAM-PS bound boronic acid **23** was added followed by 8:3 THF/EtOH. The suspension was mixed at 65 °C for up to 48 hours. It is noteworthy that it was important to use large teflon reaction vessels, with significant dead volume, in order to avoid evaporating the reaction to dryness. Afterwards, the reaction was cooled to room temperature and the resin was filtered and rinsed with the appropriate solvents. The desired arylglycine product was then cleaved off trityl resin with 5% TFA/CH₂Cl₂ to give the bis(trifluoroacetate) salt **88**. The cleaved product was very clean except for the presence of some unreacted piperazine as its bis(trifluoroacetate) salt **90**. The DEAM-PS resin does not give any artifacts upon treatment with trifluoroacetic acid in the product release step, which is important for the success of the RRTR. Average conversion levels of 79% were observed in the case of *p*-

tolylboronic acid **24** as determined by the integration of the relevant peaks in ^1H NMR spectra.

Table 4. Optimization of solvent system for the borono-Mannich RRTR of amine resin **86 and supported boronic acid **23** to give **88** (at 65 °C for 24 h).^a**

entry	solvent	conversion (%) ^b
1	7/1 DMF/EtOH	65
2	7/1 DMF/ <i>n</i> -BuOH	54
3	7/1 dioxane/ <i>n</i> -BuOH	23
4	7/1 THF/(HOCH ₂) ₂	37
5	7/1 THF/EtOH	79

^a Preparation of resin substrates, RRTR trials, and subsequent cleavage of the resin mixture were carried out as indicated in the Experimental Section. ^b Based on the relative amounts of product and bis(trifluoroacetate) salt **90**, calculated by integration of relevant signals by the ^1H NMR spectra after 24 h reaction time.

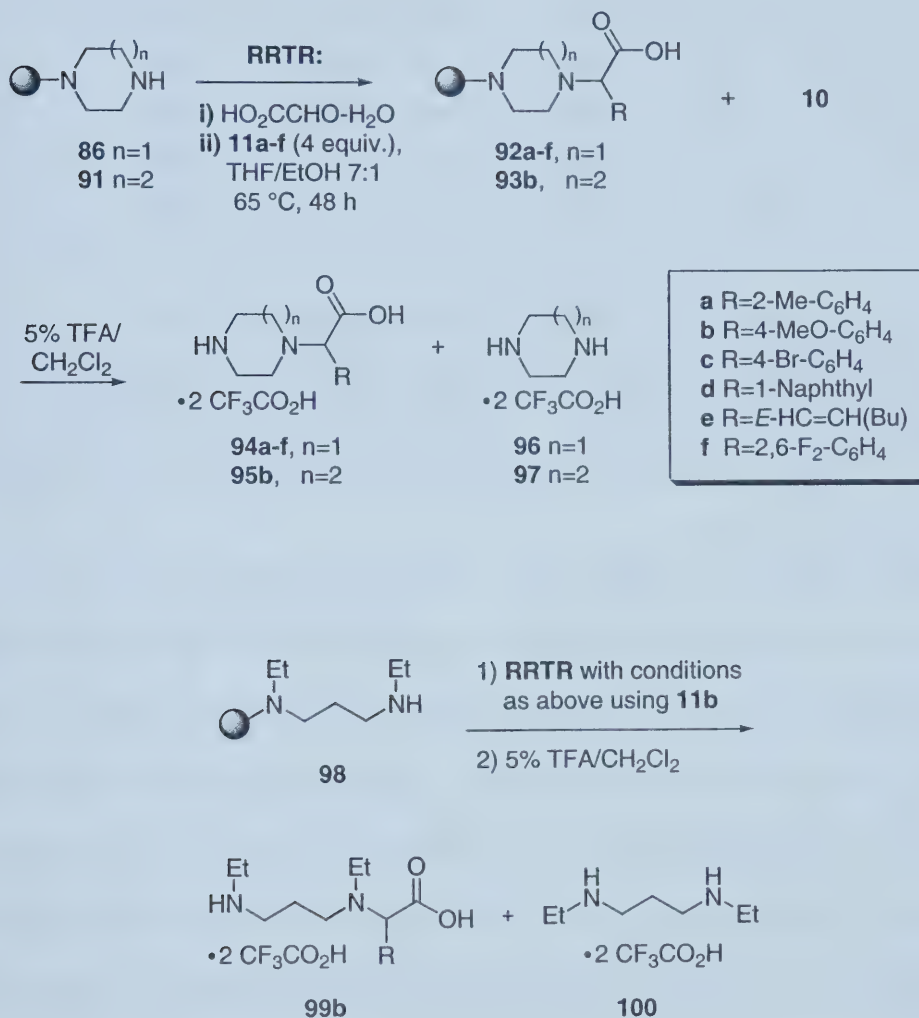


Scheme 35

The required transesterification of resin bound *p*-tolylboronic acid **23** appeared to be a dynamic equilibrium in 7/1 THF/EtOH. It was shown that the equilibrium is reached within 15 minutes of incubating the DEAM-PS supported *p*-tolylboronic acid **23** in 7/1 THF/EtOH at room temperature with approximately 40% of the *p*-tolylboronic acid being released into the solution as its corresponding ethyl boronic ester. In theory, boronic acid release should continue to occur as the boronic acid is consumed in the RRTR reaction. If the transesterification is in fact an equilibrium reaction, then incubating DEAM-PS and the free *p*-tolylboronic acid in 7/1 THF/EtOH should give the same approximate ratios of boronic acid in solution (as the ester) to boronic acid on the resin when compared to the forward direction. A control experiment for this hypothesis supported the fact that the transesterification was indeed an equilibrium reaction. This equilibrium would not be in operation if there were a large excess of water present, as the hydrolysis of DEAM-PS boronate adducts under these conditions is quantitative (*vide supra*). This hydrolysis was quite advantageous for the RRTR because an excess of water could be used in the THF rinses to get rid of the excess boronic acid from the resin mixture before cleavage of the product. A controlled experiment conducted to demonstrate that ethanol was acting as the chaperone molecule in our RRTR gave a surprising result. The RRTR was still successful in the absence of ethanol although usually with lower conversion levels than with THF/EtOH. The water introduced from the aldehyde hydrate may be sufficient to promote partial phase transfer of the supported boronic acid.

Next, the substrate generality of this new RRTR was studied (Scheme 36). Coupling several commercially available boronic acids to DEAM-PS with different electronic and steric properties were examined. Three different secondary amine resins were tested: piperazinetrityl resin **86**, homopiperazinetrityl resin **91** and linear amine resin **98**. Both amine resins **91** and **98** were made using the same general procedure described for piperazinetrityl resin **86** (*vide supra*) but with their corresponding diamines. The RRTR results are compiled in Table 5. Unfortunately, complete conversion was never obtained with any RRTR. Nonetheless, pure samples of the arylglycine products could be obtained for characterization purposes by the filtration of the unreacted secondary amines, as their corresponding bis(trifluoroacetate) diammonium salts, after precipitation using methanol and ether. The levels of conversion were generally acceptable, except for the RRTR involving electron-poor arylboronic acids. For instance, conversion values were highest for DEAM-PS supported *p*-methoxybenzene boronic acid (entries 2, 7, 8) while only a small amount of product was obtained with 2,6-difluorobenzeneboronic acid (entry 6). DEAM-PS supported alkenylboronic acids are also suitable substrates (entry 5). In addition, they can be stabilized through immobilization onto the resin as their diethanolamine adducts, whereas they slowly decompose when off solid support. This example, therefore, highlights the advantage of the RRTR strategy using DEAM-PS for handling and storage purposes. The RRTR with resin **98** was carried out to show that acyclic amines can also be used (entry 8). This success demonstrates

that, in principle, linear secondary amines such as terminal *N*-alkylamino acids could be employed.



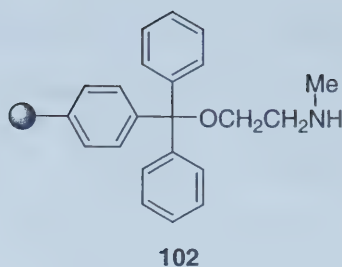
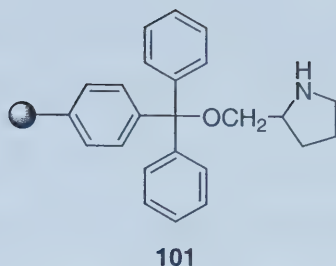
Scheme 36

Table 5. Preparation of arylglycine derivatives by borono-Mannich RRTR.^a

entry	amino resin	DEAM-PS boronate 11	product	conversion ^b (%)	yield ^c (%)
1	86	R=2-Me-C ₆ H ₄	94a	81	73
2	86	R=4-MeO-C ₆ H ₄	94b	90	> 95
3	86	R=4-Br-C ₆ H ₄	94c	21	10
4	86	R=1-Naphthyl	94d	85	90
5	86	R= <i>E</i> -HC=CH(Bu)	94e	89	> 95
6	86	R=2,6-F ₂ -C ₆ H ₃	94f	< 20	-
7	91	R=4-MeO-C ₆ H ₄	95b	95	91
8	98	R=4-MeO-C ₆ H ₄	99b	76	82

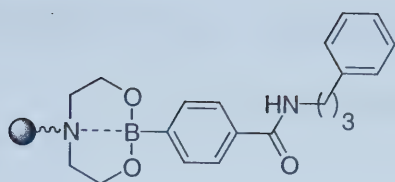
^a Preparation of resin substrates, RRTR, and subsequent cleavage of the resin mixture were carried out as indicated in the experimental section. ^b Based on the relative amounts of product and unreacted starting material resin **86**, **91** and **98** as the putative bis(trifluoroacetate) salt calculated from the integration of relevant peaks in the crude cleavage ¹H NMR spectra. ^c Yields of crude product based on ¹H NMR spectroscopic analysis with an internal standard.

Two other commercial amine resins were applied to our RRTR, prolinol 2-chlorotrityl resin **101** and *N*-methyl-2-aminoethanol 2-chlorotrityl resin **102** shown below. These examples were quickly abandoned because of formation of diastereoisomers and side products, which were difficult to interpret by NMR spectroscopy. Presumably, both resins cleave to give alcohols that could have possibly reacted in an intramolecular fashion with the carboxylic acid function of the arylglycine products resulting in the formation of a lactone. The appropriate open chain products were, however, detected by ES-MS in both cases but it was not obvious by ¹H NMR spectroscopy what the percent conversion was.

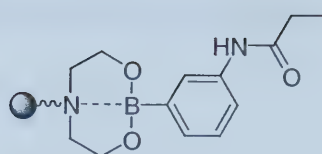


The next objective in this project was to make a library of functionalized arylboronic acids synthesized on DEAM-PS in order to demonstrate the advantages of making arylglycine libraries via a convergent RRTR method. The boronic acids synthesized on DEAM-PS could be used directly in a RRTR. Handling and cleavage of the intermediate boronic acids would be eliminated by their storage on DEAM-PS. To test in our RRTR, the resin bound boronic acids shown below were synthesized using methods described previously. Disappointingly, the RRTR with these solid supported boronic acids, piperazinetrityl resin **86** and glyoxylic acid gave low percent conversions and yields in all cases. Compound **108** gave the best result with a 33% yield of the corresponding arylglycine product. One possible reason for some of the failures may have been due to the fact that most of these boronic acids were electron poor, and it was already known that conversion levels were the highest for the electron rich DEAM-PS supported boronic acids. Although one would not expect that conversion levels would have been so low for **105**, **106** and **108**, as they should be fairly similar to the *p*-tolylboronic acid example. Boronic acid derivatives **103-107** all have a functional group that contain a nitrogen functionality, which may be detrimental in the SP borono-Mannich reaction.

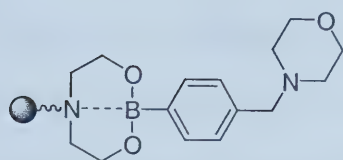
Klopfenstein and colleagues have since reported that boronic acids containing a basic nitrogen atom do not work in the Petasis reaction.^{25a} The arylglycine RRTR product from **105** would have been a tri(trifluoroacetate) salt which may have resulted in solubility and isolation problems. It would be useful to synthesize a more favored electron donating functionalized boronic acid library on DEAM-PS, which would be better suited for this borono-Mannich RRTR. Initial attempts to make a library of DEAM-PS supported aryl ether/boronic acids of type **71** (equation 4, Scheme 27) have failed. However, once a suitable DEAM-PS supported boronic acid library is in place this new borono-Mannich RRTR will be extremely useful for the convergent solid phase synthesis of large libraries of arylglycine derivatives.



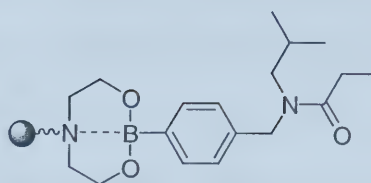
103



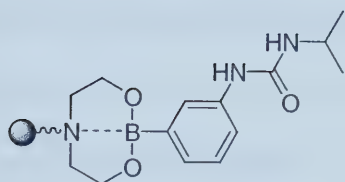
104



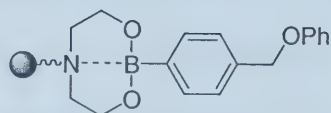
105



106



107



108

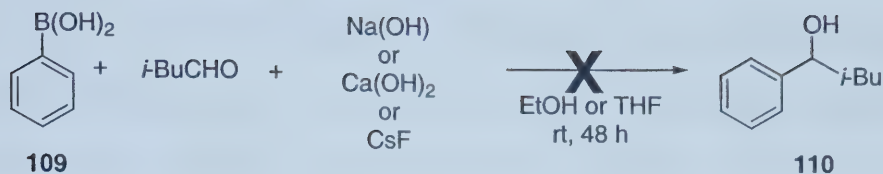
IV. Solution Phase Studies Towards Expanding the Utility of the Borono-Mannich Reaction

The three-component borono-Mannich reaction is synthetically very useful. This one-pot reaction is experimentally convenient, stereoselective, and it can lead to a diverse pool of molecules simply by varying each of its components. However, the current limitation of the borono-Mannich reaction is the need for a specific type of carbonyl component. As discussed in the introduction, the Petasis borono-Mannich reaction is currently limited to a small class of activated carbonyl compounds such as α -hydroxyaldehydes,¹² α -keto acids¹¹ and salicylaldehydes.²³ These compounds all contain a proximal hydroxyl group to the carbonyl moiety and this criteria limits the diversity of molecules that can be obtained via this three component reaction. It would be extremely useful for combinatorial library applications if the hundreds of simple readily available aldehydes could be applied to this multicomponent system. Although α -hydroxyaldehydes are very successful reagents for this reaction they are difficult to access synthetically.⁶⁰ It is believed that coordination of the α -hydroxyl group in these aldehydes to boron is important for the success of this reaction.²³ As mentioned in the introduction, this theory has been proposed for the case of salicylaldehyde. At the onset of this thesis work, it was speculated that an alternative group for boron coordination via additives or the amine component could replace the hydroxyl function of the α -hydroxyaldehyde leading

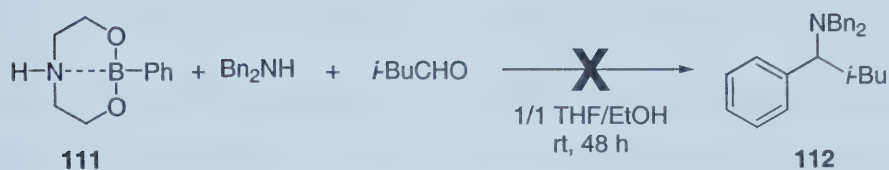
to an expanded utility of the Petasis reaction where simple aldehydes could be employed.

Several intermolecular approaches tested to meet this goal are displayed in Scheme 37. Activation of the boronic acid group was attempted via several different means by trying to weaken the carbon-boron bond of the boronic acid: with inorganic salts (equation 10), nitrogen coordination (equation 11), and having a hydroxyl group present in the amine component rather than the aldehyde component (equations 12, 13 and 14). Unfortunately, all of these attempts were met with disappointment.

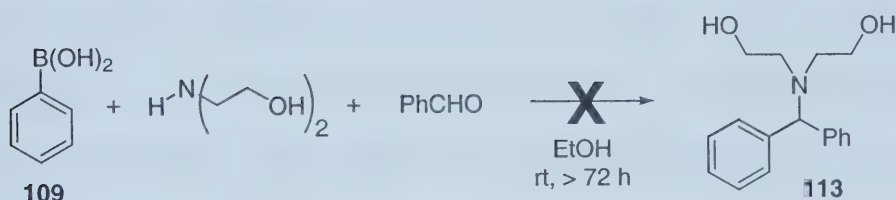
eq. 10)



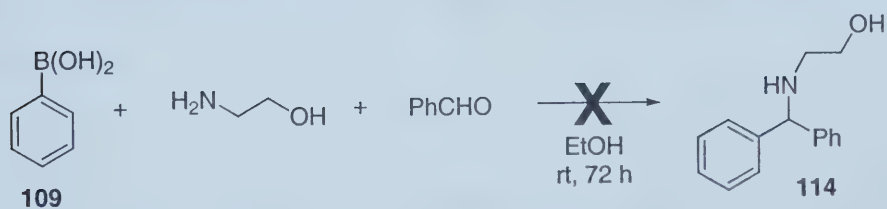
eq. 11)



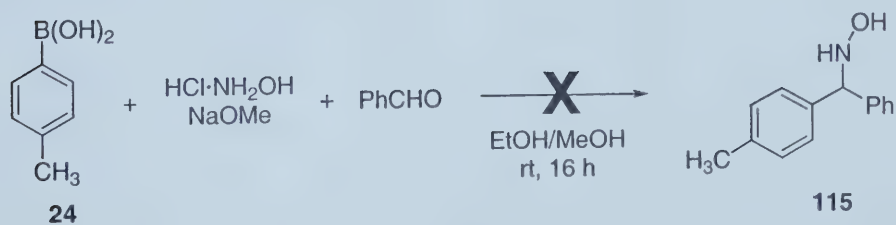
eq. 12)



eq. 13)

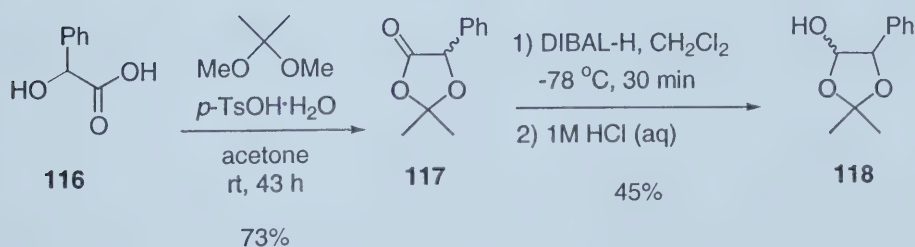


eq. 14)

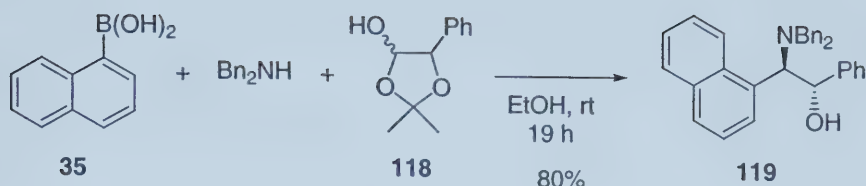


Scheme 37

Reported literature reaction conditions for the borono-Mannich reaction were followed as closely as possible for the reactions displayed in Scheme 37. Therefore, with the failure of these reactions it was decided that validation of these efforts by verification of an exact literature example of the Petasis borono-Mannich reaction was necessary.^{12a} First, α -hydroxyaldehyde equivalent **118** was made according to a literature procedure as outlined in Scheme 38.⁶⁰ Treatment of mandelic acid **116** with 2,2-dimethoxypropane in the presence of catalytic *p*-TsOH resulted in a 73% yield of intermediate **117** after purification using silica gel chromatography. DIBAL-H mediated reduction of **117** provided compound **118** in a 45% yield after flash chromatography. This compound was unstable at 4 °C for periods greater than two weeks. With α -hydroxyaldehyde equivalent **118** in hand, reproduction of Petasis' original results was possible as displayed in Scheme 39. Therefore, the attempted reactions displayed in Scheme 37 can be assumed not to be applicable to the borono-Mannich reaction with confidence.

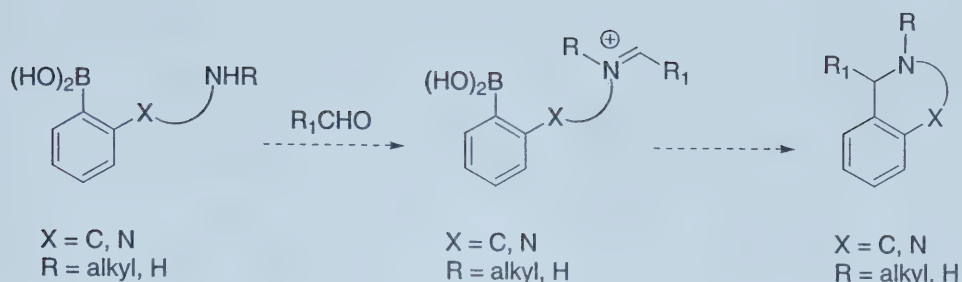


Scheme 38



Scheme 39

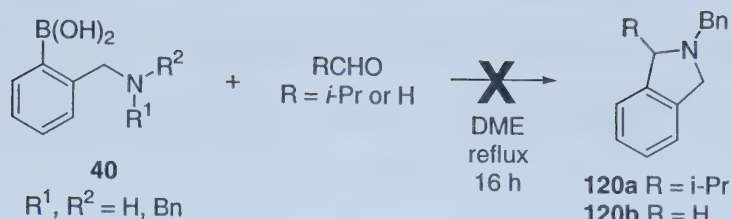
The focus was then changed to developing an intramolecular variant of the borono-Mannich reaction. Intramolecular reactions often show a greater reactivity compared to intermolecular reactions because the reactant centers are present on the same molecule. Therefore, it was believed that an intramolecular reaction could provide the required activation necessary to use easily accessible, unfunctionalized aldehydes. With this in mind, the development of a one-step, two-component, intramolecular borono-Mannich cyclization reaction was envisioned (Scheme 40). The organoboronic acid and amine function would be located on the same molecule. These two segments could then cyclize in an endo-trig fashion via the Schiff base formed by the reaction of a simple aldehyde with the free terminal amine.



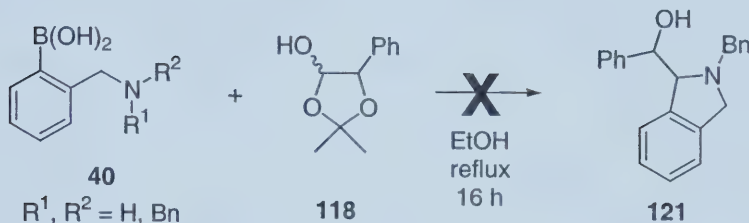
Scheme 40

Initially, compound **40** was tried for the intramolecular cyclization reaction (Scheme 41). Compound **40** was synthesized on DEAM-PS resin using reductive amination chemistry (*vide supra*). The cyclization failed using both a simple aldehyde (equation 15) and with α -hydroxyaldehyde equivalent **118** (equation 16). The cyclization of compound **40** was later attempted with glyoxylic acid, but it also failed. These results were not that surprising based on the Baldwin rules for ring closure. Baldwin's rules state that 3 to 5-*endo-trig* systems are disfavored and 6 to 7-*endo-trig* are favored.⁶¹ Therefore, it was speculated that it would be more beneficial to target reactions that resulted in either six or seven-membered ring products.

eq. 15)



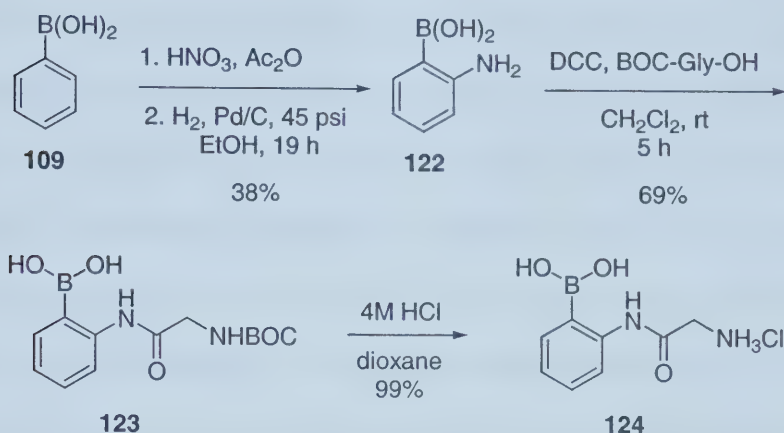
eq. 16)



Scheme 41

Therefore, what is likely a more favored 7-*endo-trig* system was modeled using boronic acid **124**. The required boronic acid **124** was synthesized as outlined in Scheme 42. Phenylboronic acid **109** was nitrated³⁷ and then subsequently reduced with hydrogen and catalytic palladium on carbon in a Parr apparatus to yield *ortho*-aminobenzeneboronic acid **122**.⁵⁵ This compound was then coupled with BOC protected glycine via a standard DCC protocol to yield amide **123** after silica gel column chromatography. This coupling reaction never went to completion but the reaction was not optimized. Removal of the BOC protective group resulted in our desired precursor **124**. This product was isolated as the amine salt whereas the Petasis reaction is usually carried out with a free amine. Thus, the literature model Petasis reaction shown in Scheme 39 was

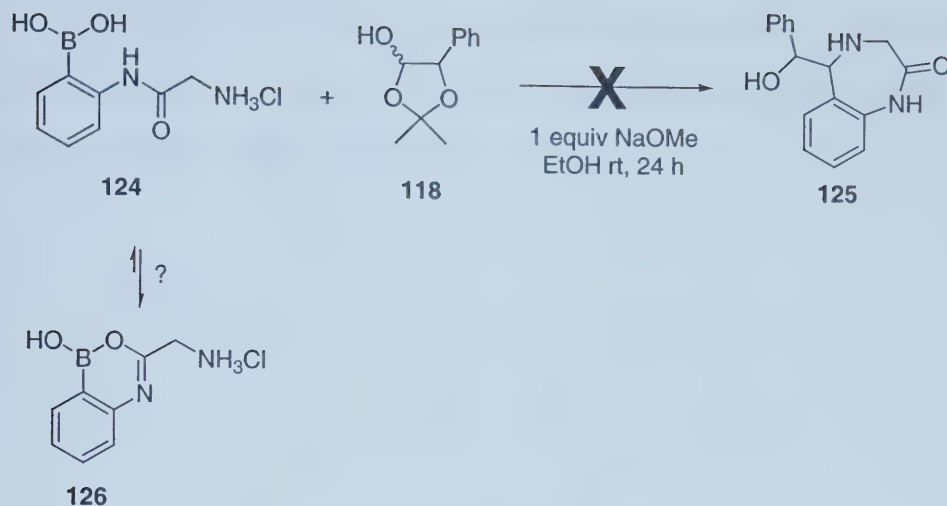
tested with *in situ* neutralization of the hydrochloride salt of dibenzylamine with sodium methoxide. This reaction was successful therefore it was believed that using the amine as its amine salt **124** would not be a problem.



Scheme 42

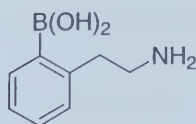
With **124** in place, an intramolecular cyclization was attempted with α -hydroxyaldehyde equivalent **118** (Scheme 43). Product **125** and its derivatives are attractive synthetic targets because they contain the framework of 1,4-benzodiazepines, which are known to have widespread biological activity.⁶² Unfortunately, this reaction was unsuccessful. Its failure may have resulted from the tendency of boronic acid **124** to exist as its monodehydrated form (**126**), as was previously postulated for anilides **59** (**B** in Figure 6) in the solid phase work with the DEAM-PS resin described in Section II. As with these anilides **59**, only the $((\text{M}-\text{H}_2\text{O})+\text{H})^+$ ion was observed by ES-MS but never the signal corresponding to the $(\text{M}+\text{H})^+$ ion of compound **124**. Structure **124** could not be

differentiated from structure **126** by IR, ^1H NMR or ^{13}C NMR spectroscopy. There was no signal corresponding to an amide proton in the ^1H NMR spectrum, which would be expected for structure **124** and not structure **126**, however the exchange of this proton could have been fast as the sample was made up in CD_3OD . The chemical shift at 167 ppm in the ^{13}C NMR spectrum is reasonable for the $\text{C}=\text{O}$ carbon in structure **124** as well as the $\text{C}=\text{N}$ carbon in structure **126**. The absorption at 1646 cm^{-1} in the IR (microscope) spectrum is also reasonable for the $\text{C}=\text{O}$ absorption expected for compound **124** as well as the $\text{C}=\text{N}$ absorption expected for compound **126**. The presence of an N-H absorption expected in the IR spectrum of compound **124** and not compound **126** is not conclusive because of the very intense O-H absorption ($3500\text{-}2000\text{ cm}^{-1}$) in the same region of the spectrum.

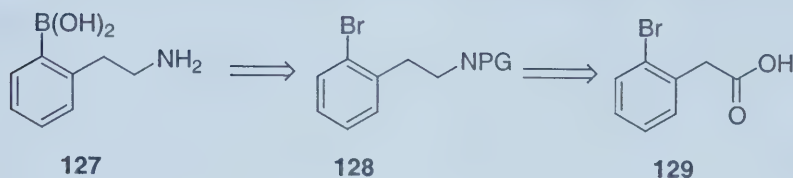


Scheme 43

To further investigate the feasibility of a borono-Mannich cyclization reaction, the synthesis of **127** was proposed. This boronic acid would result in the formation of a six-membered ring when used for an intramolecular borono-Mannich reaction. This boronic acid, without the presence of the *ortho* anilide function, would not have the possibility to dehydrate as did substrate **124**. The result of the reaction with substrate **127** would help to determine if dehydration was in fact the cause of failure for the above cyclization reaction.

**127**

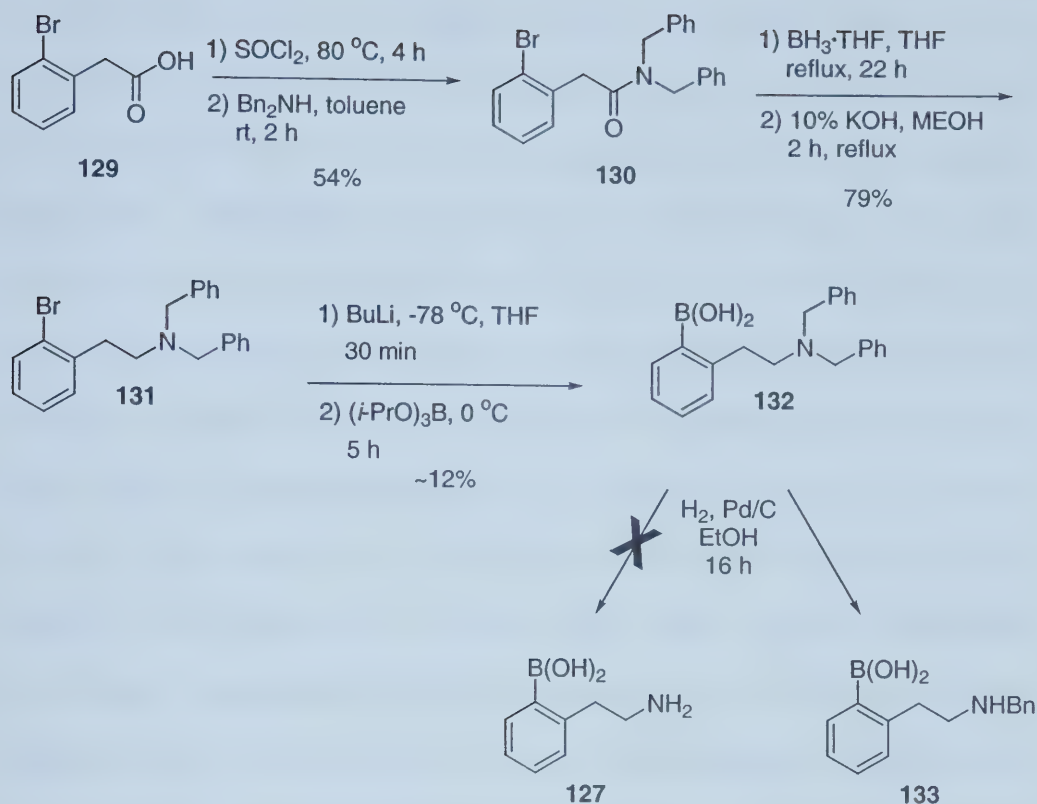
From a retrosynthetic perspective, boronic acid **127** may be formed from its corresponding arylbromide **128** (Scheme 44). The amino side chain of **127** can be derived from 2-bromophenylacetic acid **129**.



Scheme 44

The synthesis of boronic acid **127** is outlined in Scheme 45. Conversion of carboxylic acid **129** to amide **130** via the acyl chloride was achieved according to a modified literature procedure,⁶³ in 54% yield after purification. Benzyl groups were chosen as the amine protective group because they are removed with hydrogen and catalytic palladium on carbon, conditions that were shown compatible with the boronic acid functionality of *ortho*-nitrobenzeneboronic acid as shown in Scheme 42. Reduction of amide **130** with $\text{BH}_3\cdot\text{THF}$ gave **131** in 79% yield.⁶⁴ Reaction of the bromide in **131** with two equivalents of butyllithium and triisopropylborate resulted in a low, non optimized yield of boronic acid **132**, which was purified by scavenging using the DEAM-PS resin. The use of only one equivalent of butyllithium and one equivalent of TMEDA resulted in complete recovery of the starting bromide **131** after work-up determined by TLC, ES-MS

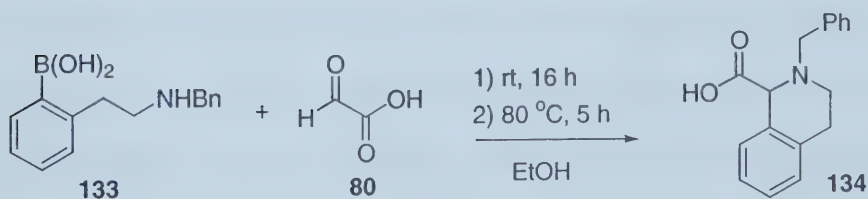
and ^1H NMR spectroscopy. Formation of the Grignard reagent from **131** was also attempted as a route for the synthesis of boronic acid **132**, however the reaction of **131** with magnesium failed to initiate. The deprotection of dibenzylamine **132** using hydrogen and catalytic palladium on carbon did not provide primary amine **126** but rather afforded the mono-benzylamine **133** as the major product.



Scheme 45

The deprotection of amine **132** was conducted on a small scale (0.04 mmol) and crude product **133** was therefore not purified. The Petasis reaction is known to proceed with both primary and secondary amine and therefore it was decided that **133** could be used directly in the borono-Mannich cyclization reaction (Scheme 46). Glyoxylic acid **80** was chosen as the model aldehyde component as it worked well in the borono-Mannich RRTR of section III and it is commercially available. Thus, crude substrate **133** and glyoxylic acid were stirred in ethanol and after sixteen hours an aliquot was taken from the reaction mixture for ES-MS analysis. At this time, signals corresponding to both product

134 and starting material **133** were observed in the ES-MS spectrum. The mixture was then refluxed for an additional five hours at which time none of **133** was detected by ES-MS, but just the base peak corresponding to the expected product **134**. HPLC-MS analysis of the crude reaction mixture showed that product **134** was the main component (Figure 9). The ^1H NMR spectroscopic analysis of the crude reaction mixture was in reasonable agreement with the formation of product **134**. Although these are only preliminary results it appears that a 6-*endo-trig* Petasis cyclization reaction is indeed possible! As a next step, it needs to be determined if the reaction works with simple, unactivated aldehydes. One attempt of an intramolecular Petasis cyclization with boronic acid **133** and “unactivated” benzaldehyde was unsuccessful using the reaction conditions shown in Scheme 46. However, work is ongoing by the Hall research group to achieve a successful intramolecular borono-Mannich reaction with “normal” aldehydes. Success of the cyclization reaction with “normal” aldehydes would be a significant extension of the borono-Mannich reaction.



Scheme 46

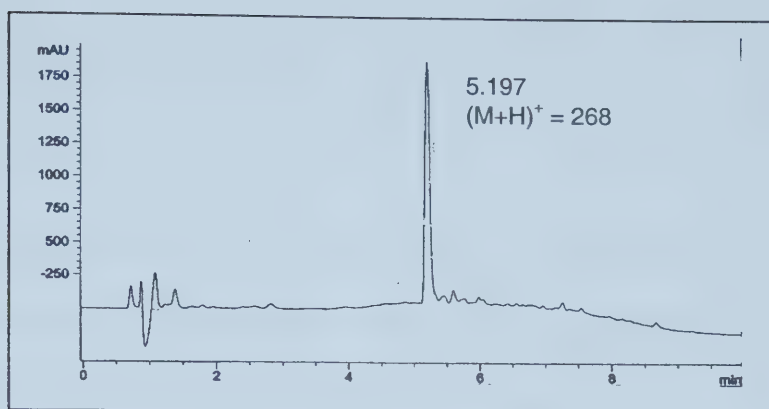
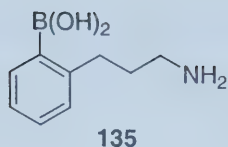


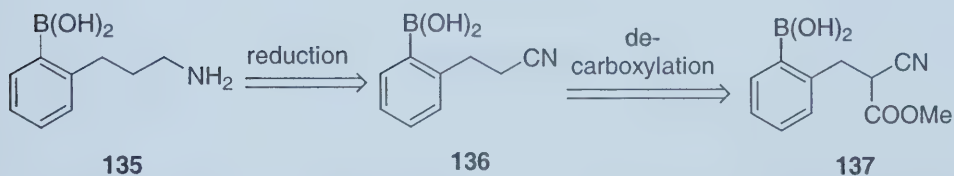
Figure 9. HPLC and ES-MS analysis of crude compound 134

The success of the previous reaction hints that dehydration may have indeed caused the cyclization of boronic acid **124** in Scheme 43 to fail. To further confirm that dehydration was in fact the problem, the cyclization reaction shown in Scheme 43 would need to be repeated with glyoxylic acid **80** rather than using the α -hydroxyaldehyde equivalent **118** as the aldehyde component in order to establish direct comparison. Also, the hypothetical product of the cyclization reaction with boronic acid **124** is a seven-membered ring whereas the product of the above cyclization was a six-membered ring and therefore, they cannot be directly compared. One also has to keep in mind that boronic acid **124** contains an amide whereas **133** does not which make the electronics of their corresponding cyclization reactions different. Regardless, boronic acid **135** was targeted to further evaluate the cyclization reaction.

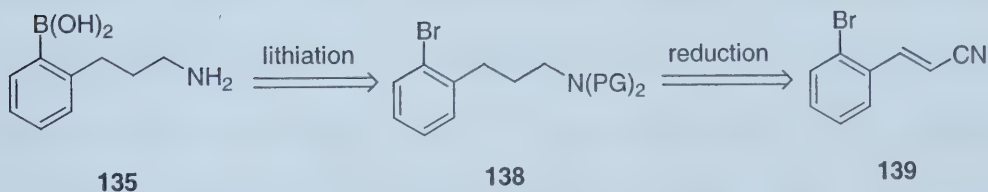


The synthesis of boronic acid **135** was originally envisioned by two methods (Scheme 47): the decarboxylation/reduction sequence (equation 17) or via a lithiation/reduction sequence (equation 18).

eq. 17)



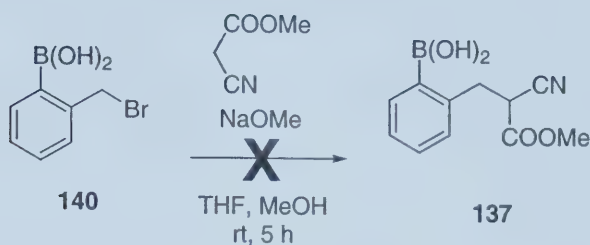
eq. 18)



Scheme 47

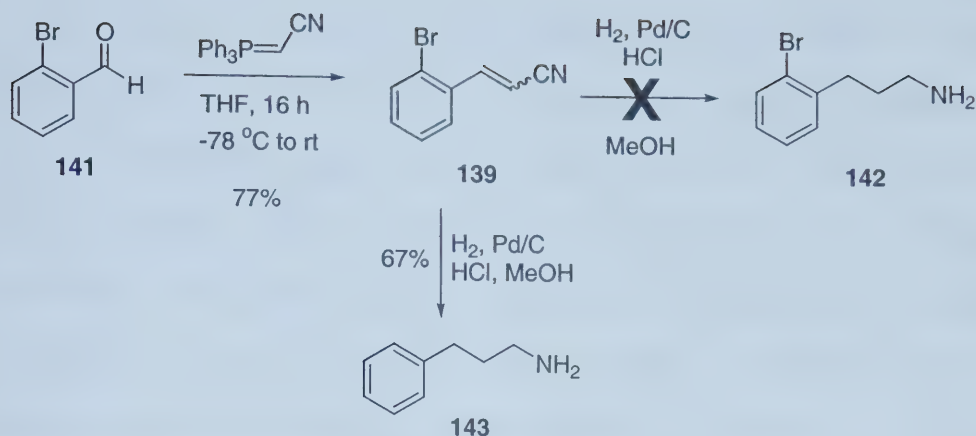
The attempted synthesis of boronic acid **137** from bromide **140** is shown in Scheme 48. Unfortunately, the reaction resulted in no product formation. However, a similar sequence on the corresponding pinacol ester of boronic acid **140** provided a successful reaction. Therefore, the reaction conditions below are not compatible with the free boronic acid. The approach displayed in equation 17

was abandoned because the pinacol ester of **137** could not be cleaved to give the free boronic acid, which was needed in the end to test the borono-Mannich reaction.



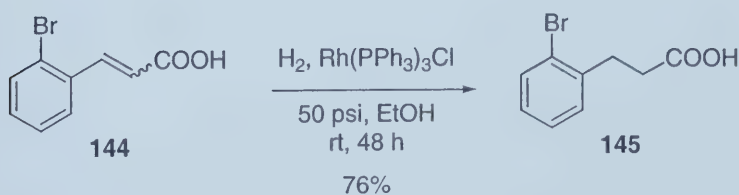
Scheme 48

Nitrile **139** was synthesized in good yield via a Wittig reaction on commercially available **141** but its subsequent reduction with hydrogen and catalytic palladium on carbon in the presence of HCl ⁶⁵ did not yield the desired aryl bromide **142** (Scheme 49). Instead, the reduction resulted in protonolysis of the aromatic bromide and the undesired amine **143** was isolated in 67% yield after work-up. Reduction of nitrile **139** with LiAlH_4 was also unsuccessful. Hence, the sequence shown in equation 18 was not useful for the synthesis of boronic acid **135** and also had to be abandoned.



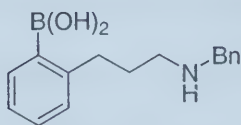
Scheme 49

It was anticipated that boronic acid **135** could be made via a route similar to the one proposed in Scheme 44 for the synthesis of boronic acid **127**. Carboxylic acid **145** was synthesized in a 76% yield by reduction of *ortho*-bromocinnamic acid **144** according to a literature procedure,⁶⁶ using Wilkinson's catalyst as outlined in Scheme 50.



Scheme 50

In theory, with carboxylic acid **145** in hand, boronic acid **146** shown below should be accessible via the same set of reactions as used for the synthesis of boronic acid **133** (Scheme 45). The synthesis of boronic acid **146** is ongoing in the Hall laboratories. Once it is obtained, it will be tested in the borono-Mannich reaction with both glyoxylic acid and “non activated” benzaldehyde to further evaluate the cyclization reaction. If the cyclization reaction of **146** were successful it would further support that dehydration was most likely the problem for the cyclization of boronic acid **124**. Although the cyclization reaction with boronic acid **124** would still need to be tested with glyoxylic acid to ascertain this hypothesis.

**146**

V. General Conclusion

N,N-Diethanolaminomethyl polystyrene (DEAM-PS), a novel solid support for boronic acids, has been evaluated for the immobilization, cleavage, derivatization and RRTR of this class of compounds. The immobilization of arylboronic acids onto DEAM-PS is achieved in anhydrous solvents at room temperature. Their subsequent release is possible using wet THF (5% H₂O/THF). UV spectroscopic studies indicated that the attachment and hydrolysis of boronic acids to and from DEAM-PS occur under a rapidly reached equilibrium. Greater than 32 equivalents of water is required to obtain near quantitative release of boronic acids from DEAM-PS. A wide range of chemistry is compatible with the DEAM-PS boronate linkage provided that anhydrous conditions are employed. Several boronic acid derived amines, anilides, and ureas can be synthesized. As well, the multi-component Ugi reaction, derivatization of multifunctional arylboronic acids and sequential reactions are possible on DEAM-PS. Therefore, this resin has led to the synthesis of many new boronic acids which would have been otherwise difficult to obtain via solution phase methods. It was also shown that DEAM-PS supported boronic acids have further synthetic applications via the development of a borono-Mannich resin-to-resin transfer reaction (RRTR) to make arylglycine derivatives. Conceptually, this convergent multi-resin system is useful for large library synthesis, avoiding cleavage and transfer operations compared to a linear, "one resin" approach. In summary, DEAM-PS has been shown to be an invaluable tool for synthetic chemists involved in research dealing with organoboronic acids.

Preliminary solution phase results indicated that an intramolecular Petasis borono-Mannich reaction is possible. Cyclization with glyoxylic acid to yield a 6-membered 1,2,3,4-tetrahydro-isoquinoline ring product was successful. This constitutes the first report of an intramolecular Petasis reaction. Building upon these promising results, the Hall research group will keep studying the scope of this reaction and its applications.

VI. Experimental Section

1. General

All starting boronic acids employed are commercially available (Lancaster, Frontier Scientific, and Combi-Blocks) unless otherwise stated and were used without purification. Starting resins were purchased from Rapp-Polymere (Tübingen, Germany) and Nova-Biochem (LaJolla, CA) unless otherwise stated. In most cases, the loading value stated by the supplier was used. Solid-phase reactions that required heating were performed in glassware silanized by treatment with 20% TMSCl/toluene for greater than 12 hours. Those done at room temperature were agitated inside polypropylene (pp) filter vessels purchased from either Bio Rad (Hercules, California) or International Sorbent Technology Ltd. (Hengoed, UK). Solid phase reactions were carried out on a vortexer or a mechanical shaker. Resin rinses were carried out on a vortexer for ~ one minute each. For RRTR's, runs were done in 10 mL teflon fritted vessels on a Quest 210 instrument with solvent wash unit (Argonaut Technologies), or in a round bottom flask fitted with a condenser. Solution phase processes involving air or moisture sensitive reactants and/or requiring anhydrous conditions were performed under a positive pressure of pre-purified nitrogen using flame dried glassware. THF and Et₂O for reactions and solid phase cleavage operations (including resin washes) were dried by distillation over sodium/benzophenone ketyl under a nitrogen atmosphere and used the same

day. Dichloromethane, toluene and methanol were distilled over calcium hydride under a nitrogen atmosphere. Anhydrous NMP and DMF were obtained commercially. Aldrich spectrochemical grade TFA was dried and distilled over P_2O_5 prior to use. Concentration under reduced pressure refers to the removal of solvents using a Büchi rotary evaporator below 40 °C. Drying samples under high vacuum refers to pressures less than 0.1 mm Hg.

Reactions and fractions from column chromatography were monitored by thin layer chromatography (TLC) whenever possible using Merck glass-backed plated precoated with 0.25 mm of silica gel (Merck 60F-254). One or more of the following methods were used for visualization: UV fluorescence, $KMnO_4$ staining, or exposure to 5% phosphomolybdic acid in EtOH. Flash chromatography was performed according to the Still procedure,⁶⁷ using silica gel 60 (230-400 mesh) obtained from Silicycle, Québec.

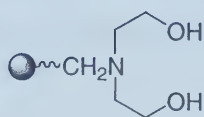
Chemical yields of boronic acid products via the DEAM-PS resin were compiled as an average of mass balance (assuming dehydration to the corresponding anhydrides ($FW = FW - H_2O$) and internal standardization by 1H NMR spectroscopy). Ethyl acetate was used as an internal standard and it was found to provide very consistent values with a 15 second relaxation delay. Purity analysis was estimated by 1H and ^{13}C NMR spectroscopy according to the following scheme: greater than 95%: no unidentified peaks; 95%: minor amounts of barely measurable impurities; other percentages were based on the relative measure of peak heights and integrals from signals of product compared to signals from starting boronic acid and by-products. For reactions carried out in

NMP, minor residual amounts of solvent sometimes present in NMR spectra were not accounted for in the evaluation of purity. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM-300 and INOVA Varian 300, 400 and 500 MHz instruments. ^1H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet, qn, quintet; sx, sextet; h, heptet; m, multiplet; and br, broad), coupling constant(s) in Hertz (Hz), and number of protons. Due to their very low intensity, ^{13}C signals arising from the quaternary carbon bearing the boronic acid group were usually missing and were therefore not listed. They were sometimes observed as broad signals in ^{13}C BB NMR spectra but were never observed in the corresponding ^{13}C APT NMR experiments. Similarly, the ^{13}C signals arising from quaternary carbons bearing a carbonyl substituent or of TFA salts ($-\text{CF}_3$) were sometimes missing. Low resolution electrospray mass spectra were acquired using atmospheric pressure ionization (API) with a quadrupole mass analyser (positive mode). High-resolution (HRMS) analysis were obtained on a time-of-flight instrument. A 1:1 mixture of MeCN/ H_2O was used as the solvent for mass spectral analysis of boronic acids. It was important not to use alcohols as solvents for the mass spectral analysis of boronic acids in order to avoid observing their corresponding boronate esters. UV analysis was carried out using a Varian Cary 400 UV-visible spectrophotometer. IR spectra were acquired on a Nicolet Magna 750 IR Spectrophotometer and a Nic-Plan IR Microscope. Microanalyses were determined on a Perkin Elmer 240 or a Carlo Erba 1180 elemental analyzer. All

literature compounds had ^1H NMR and mass spectra consistent with the reported data.

2. Experimental Procedures and Spectral Data

N,N-diethanolaminomethyl polystyrene (DEAM-PS) (**10**).

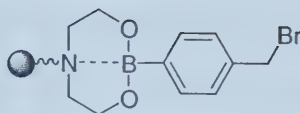


Chloromethyl polystyrene resin (3.00 g, 3.72 mmol, theor. loading: 1.24 mmol g^{-1} , 200-400 mesh) was weighed into a 70 ml pp reaction vessel and swollen in dry NMP (32 mL). Diethanolamine (7.13 mL, 74.4 mmol) was added and the mixture was vortexed for a short time. NaI (2.79 g, 18.6 mmol) was added as a solid and the resin suspension was shaken at rt for greater than 48 h. The reaction mixture was drained, and the resin was rinsed with 2:1 THF/ H_2O (3 \times), 1:1 DMF/ Et_3N (3 \times), dry THF (3 \times), and CH_2Cl_2 (5 \times). The resin was then dried under high vacuum for greater than 24 h to afford a white resin (3.03 g, theoretical: 3.26 g, theor. loading: 1.14 mmol g^{-1}).

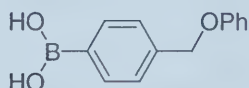
Typical procedure for the immobilization and cleavage of a boronic acid to and from DEAM-PS: Preparation of **23.** *p*-Tolylboronic acid **24** (20 mg, 0.15 mmol, 1.3 equiv) and THF (1.5 mL) were added to DEAM-PS **10** (102 mg, 0.117

mmol, 1 equiv, exper. loading: 1.15 mmol g⁻¹) in a pp reaction vessel. The reaction suspension was shaken at rt for 1 h and the pp vessel was drained. The resin was then washed with dry THF (3×, 2 mL). The resin-bound boronic acid **23** was cleaved by vortexing the resin with 5% H₂O/THF (2 mL) for 1 min at rt. The product-containing solution was drained and the resin was washed with 5% H₂O/THF (3×, 2 mL). The filtrates were combined, concentrated under reduced pressure and dried under high vacuum overnight to afford *p*-tolylboronic acid **24** as a white solid (12 mg, 87% yield by mass; 91% yield by ¹H NMR with EtOAc int. std.).

UV spectroscopic studies conducted on the cleavage of *p*-tolylboronic acid from DEAM-PS (10). A calibration graph (absorbance at 225 nm vs concentration (M)) was made using *p*-tolylboronic acid **24**. DEAM-PS supported *p*-tolylboronic acid **23** (330 mg, 0.278 mmol, obs. loading: 0.842 mmol g⁻¹) was weighed into a 20 mL pp reaction vessel and swollen in dry THF (5 mL). A 50 μL aliquot was diluted to 25 mL with dry THF for UV analysis. Then resin **23** was cleaved with a sequential addition of water. First, H₂O (10 μL, 2 equiv) was added and the pp vessel was shaken for 1 min and a 50 μL aliquot was diluted to 25 mL with dry THF for UV analysis. Next, the previous sequence was repeated for 4 (20 μL total), 8 (40 μL total), 16 (80 μL total), 32 (160 μL total), 64 (320 μL total) and 128 (640 μL total) equivalents of water. Results are displayed in Figure 5.

DEAM-PS supported 39.

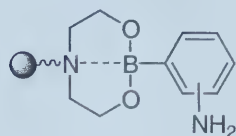
This resin was prepared according to the general procedure for the immobilization of a boronic acid to DEAM-PS as described above. Instead of being cleaved, this resin was dried under high vacuum for > 24 h.

Preparation of 4-(Phenoxymethyl)phenylboronic acid (43).

Phenol (41 mg, 0.44 mmol) was weighed into a round bottom flask and dissolved in dry NMP (1.5 mL). Dry 95% NaH (18 mg, 0.73 mmol) was added at 0 °C and the suspension was stirred for 30 min. Resin **39** (325 mg, 0.291 mmol, theor. loading 0.895 mmol g⁻¹) was weighed into a 20 mL pp vessel and swollen in NMP (4 mL). The PhONa suspension was added to the resin followed by nBu₄NI (54 mg, 0.15 mmol) and the reaction was shaken for 24 h at rt. The reaction suspension was drained and the resin was rinsed with DMF (3 × 4 mL), THF (3 × 4 mL) and CH₂Cl₂ (3 × 4 mL). The product was cleaved from the resin using standard conditions and the combined filtrates were concentrated. Filtration of

the product through a pad of silica gel using 10% MeOH/CH₂Cl₂ followed by concentration yielded a white solid (37 mg, 61% yield by mass; 42% yield by ¹H NMR with EtOAc int. std.): ¹H NMR (300 MHz, 5% D₂O in CD₃OD) δ; 7.73 (br d, *J* = 8 Hz, 2H), 7.40-7.37 (d, *J* = 8.0 Hz, 2H), 7.27-7.21 (m, 2H), 6.98-6.88 (m, 3H), 5.06 (s, 2H); ¹³C NMR (75 MHz, 5% D₂O in CD₃OD) δ 164.9, 145.5, 139.8, 135.3, 132.4, 126.8, 120.7, 75.7; IR (microscope) 3427, 3039, 2920, 2869, 1612, 1598 cm⁻¹; LRMS (ES, *m/z*, negative mode with NH₄F postcolumn) 249 (M+F)⁻.

DEAM-PS supported 47, 48 and 49.



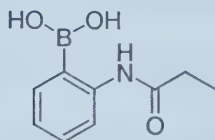
47 *o*-, 48 *m*-, 49 *p*-

These resins were prepared according to the general procedure for the immobilization of a boronic acid to DEAM-PS as described above. Instead of being cleaved, these resins were dried under high vacuum for > 24 h.

Typical procedure for the formation of anilides using PyBOP: Preparation of 60a. Resin **48** (102 mg, 0.0965 mmol, theor. loading: 0.946 mmol g⁻¹) was added to a 10 mL polypropylene vessel and swollen in NMP (1.5 mL). PyBoP (100 mg, 0.193 mmol), DIPEA (67 μL, 0.39 mmol), and propionic acid (14 μL, 0.19 mmol) were added in the given order and the reaction vessel was shaken

for 19 h at rt. The suspension was drained, and the resin was rinsed with NMP (3×), CH₂Cl₂ (5×), and THF (3×). The product was then cleaved from the resin using the standard conditions described above. The product rinses were combined, concentrated under reduced pressure and dried under high vacuum overnight to afford a yellow solid (13 mg, 76% yield by mass; 68% yield by ¹H NMR with EtOAc int. std.). See characterization below.

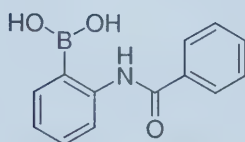
***N*-(Propionyl)-2-aminophenylboronic acid (**59a**).**



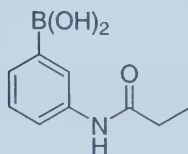
White solid (61% yield by mass): ¹H NMR (300 MHz, CD₃OD) δ 7.46-7.43 (m, 1H), 7.31-7.20 (m, 2H), 7.03-7.00 (m, 1H), 2.66 (q, *J* = 8 Hz, 2H), 1.33 (t, *J* = 8 Hz, 3H); IR (microscope) 3100-2400, 3000, 2979, 1640, 1601 cm⁻¹; HRMS (ES, *m/z*) calcd for C₉H₁₂BNO₃Na (M+Na)⁺ 216.0802, found 216.0806. A ¹³C NMR spectrum of **59a** could not be obtained due to low solubility. Therefore, compound **59a** was derivatized as its pinacol ester **62a** in order to obtain a ¹³C NMR spectrum. Compound **59a** was cleaved from the DEAM-PS resin **10** with 10% pinacol/THF and purified by flash chromatography on silica gel using 1/1 ethyl acetate/CH₂Cl₂ as an eluent affording **62a** as a white solid. ¹H NMR (500 MHz, CD₃OD) δ 8.16 (br d, *J* = 6 Hz, 1H), 7.71-7.70 (m, 1H), 7.35 (t, *J* = 8 Hz, 1H), 7.05 (t, *J* = 7 Hz, 1H), 2.29 (q, *J* = 8 Hz, 2H), 1.35 (s, 12H), 1.18 (t, *J* = 8 Hz,

3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 143.4, 135.6, 131.9, 123.4, 118.6, 83.7, 30.6, 25.1, 9.4.

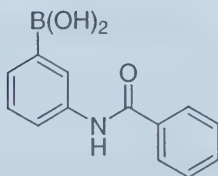
***N*-(Benzoyl)-2-aminophenylboronic acid (**59b**).**



White solid (60% yield by mass): ^1H NMR (500 MHz, CD_3OD) δ 8.18-8.16 (m, 2H), 7.76-7.73 (m, 1H), 7.65-7.62 (m, 2H), 7.53-7.51 (m, 1H), 7.37-7.28 (m, 3H); IR (microscope) 3203, 3063, 2958, 1624, 1602 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{12}\text{BNO}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 264.0802, found 264.0798. A ^{13}C NMR spectrum of **59b** could not be obtained due to low solubility. Therefore, compound **59b** was derivatized as its pinacol ester **62b** in order to obtain a ^{13}C NMR spectrum. Compound **59b** was cleaved from the DEAM-PS resin **10** with 10% pinacol/THF and purified by flash chromatography on silica gel using ethyl acetate as an eluent to furnish **62b** as a white solid: ^1H NMR (500 MHz, CD_3OD) δ 8.70 (d, J = 8 Hz, 1H), 8.02 (m, 2 H), 7.80 (m, 1 H), 7.54-7.45 (m, 4 H), 7.08 (m, 1H), 1.39 (s, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.2, 144.9, 136.2, 135.3, 133.0, 131.6, 128.5, 127.2, 123.0, 119.1, 84.5, 24.9.

***N*-(Propionyl)-3-aminophenylboronic acid (60a).**

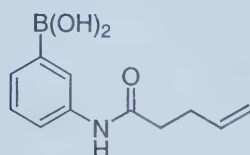
Yellow solid (76% yield by mass; 68% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.77 (s, 1 H), 7.60 (d, J = 8 Hz, 1 H), 7.45 (d, J = 7 Hz, 1 H), 7.26 (t, J = 8 Hz, 1 H), 2.38 (q, J = 8 Hz, 2 H), 1.19 (t, J = 8 Hz, 3 H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 175.6, 139.0, 130.7, 129.0, 126.9, 123.5, 31.0, 10.3; IR (microscope) 3303, 3057, 2980, 1665, 1615 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_9\text{H}_{12}\text{BNO}_3$ ($\text{M}+\text{H}$) $^+$ 194.0983, found 194.0981.

***N*-(Benzoyl)-3-aminophenylboronic acid (60b).**

Beige solid (86% yield by mass; 77% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.93-7.90 (m, 3 H), 7.73 (d, J = 8 Hz, 1 H), 7.60-7.47 (m, 4 H), 7.34 (t, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 169.0, 142.1 (broad), 138.9, 136.2, 132.9, 131.3, 129.7, 129.1, 128.6, 128.0,

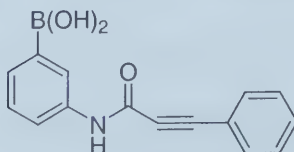
124.7; IR (microscope) 3317, 3066, 3045, 1645, 1603, 1580 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{13}\text{BNO}_3$ ($\text{M}+\text{H}$) $^+$ 242.0983, found 242.0984.

***N*-(3'-Butenylcarbonyl)-3-aminophenylboronic acid (60c).**



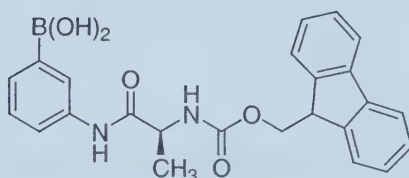
White solid (74% yield by mass, 66% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.76 (s, 1H), 7.59 (d, J = 8 Hz, 1H), 7.46 (d, J = 7 Hz, 1H), 7.27 (t, J = 8 Hz, 1H), 5.94-5.81 (m, 1H), 5.12-4.97 (m, 2H), 2.47-2.41 (m, 4H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 174.0, 138.9, 138.2, 135.3 (broad), 130.8, 129.0, 126.9, 123.6, 116.0, 37.2, 30.8; IR (microscope) 3319, 3079, 2978, 1660, 1644, 1606, 1532 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{11}\text{H}_{15}\text{BNO}_3$ ($\text{M}+\text{H}$) $^+$ 220.1145, found 220.1146.

***N*-(2'-Phenylethynylcarbonyl)-3-aminophenylboronic acid (60d).**

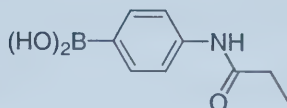


Yellow solid (76% yield by mass, 73% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.84 (br s, 1H), 7.69-7.67 (m, 1H), 7.63-7.60 (m, 2H); 7.54-7.50 (m, 1H), 7.48-7.39 (m, 3H), 7.36-7.30 (m, 1H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 153.5, 143.9 (broad), 138.4, 133.6, 131.6, 131.5, 129.8, 129.3, 126.7, 123.7, 121.2, 87.0, 84.0; IR (microscope) 3263, 3056, 2211, 1642, 1583 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{15}\text{H}_{12}\text{BNO}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 288.0808, found 288.0806.

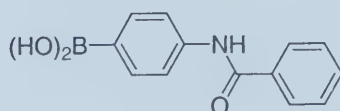
***N*-[*N*-(9-Fluorenylmethoxycarbonyl)-L-alaninyl]-3-aminophenylboronic acid (60e).**



Yellow solid (53% yield by mass, 48% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in THF-d_8) δ 7.82 (m, 2H), 7.73 (d, $J = 7\text{ Hz}$, 2H), 7.63 (t, $J = 7\text{ Hz}$, 2H), 7.47 (d, $J = 7\text{ Hz}$, 1H), 7.32-7.14 (m, 5H), 4.35 (q, $J = 7\text{ Hz}$, 1H), 4.29-4.14 (m, 3H), 1.45 (d, $J = 7\text{ Hz}$, 3H); ^{13}C NMR (75 MHz, 5% D_2O in THF-d_8) δ 172.1, 157.2, 145.3, 145.1, 142.2, 139.2, 141.4 (broad), 130.4, 128.4, 127.9, 126.2, 126.1, 122.3, 120.6, 51.9, 48.2, 19.1; IR (microscope) 3307, 3065, 2977, 1673, 1610 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{24}\text{H}_{23}\text{BN}_2\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 453.1598, found. 453.1598.

***N*-(Propionyl)-4-aminophenylboronic acid (61a).**

Cream-colored solid (61% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.73-7.66 (m, 2H), 7.54-7.49 (m, 2H), 2.38 (q, J = 8 Hz, 2H), 1.18 (t, J = 8 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 175.9, 141.6, 135.6, 130.0 (broad), 120.1, 31.1, 10.3; IR (microscope) 3306, 3044, 2979, 1666, 1594 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_9\text{H}_{13}\text{BNO}_3$ ($\text{M}+\text{H}$) $^+$ 194.0983, found 194.0985.

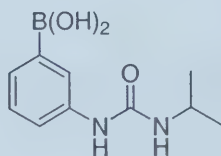
***N*-(Benzoyl)-4-aminophenylboronic acid (61b).**

White solid (47% yield by mass, 45% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.92-7.89 (m, 2H), 7.76-7.73 (m, 2H), 7.69-7.64 (m, 2H), 7.60-7.47 (m, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 169.1, 136.1, 135.6, 133.0, 129.7, 128.6, 121.1; IR (microscope) 3313, 3040,

1650, 1601, 1588 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{12}\text{BNO}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ 264.0808, found 264.0803.

Typical procedure for the formation of ureas: Preparation of 64a. In a 10 mL pp reaction vessel, resin **48** (104 mg, 0.10 mmol, theor. loading: 0.96 mmol g^{-1}) was swollen in CH_2Cl_2 (2 mL). Isopropylisocyanate (20 μL , 0.20 mmol) was added and the vessel was shaken for 7 h at rt. The suspension was drained, and the resin was rinsed with CH_2Cl_2 (8×2 mL). The product was then cleaved from the resin using the standard conditions described above. The combined filtrates were concentrated under reduced pressure and dried under high vacuum overnight to afford a brown solid (16 mg, 76% yield by mass; 66% yield by ^1H NMR with EtOAc int. std.). See characterization below.

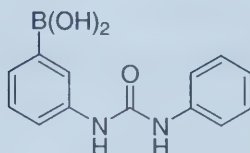
***N*-(iso-Propylaminocarbonyl)-3-aminophenylboronic acid (64a).**



Brown solid (76% yield by mass; 66% yield by ^1H NMR with EtOAc int std): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.58 (s, 1 H), 7.43 (d, J = 8 Hz, 1 H), 7.35 (d, J = 7 Hz, 1 H), 7.22 (t, J = 8 Hz, 1 H), 3.87 (h, J = 7 Hz, 1 H), 1.16 (d, J = 7 Hz, 6 H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 157.9, 140.1, 129.1, 129.0, 125.8, 122.6, 42.9, 23.4;⁶⁸ IR (microscope) 3347, 3036, 2985, 1639, 1568, 1343

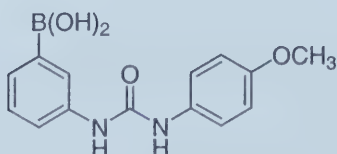
cm^{-1} ; HRMS (ES, m/z) calcd for HRMS (ES, m/z) calcd for $\text{C}_{10}\text{H}_{16}\text{BN}_2\text{O}_3$ ($\text{M}+\text{H}$)⁺ 223.1248, found 223.1250.

***N*-(Phenylaminocarbonyl)-3-aminophenylboronic acid (64b).**



Beige solid (79% yield by ^1H NMR with EtOAc int std): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.67 (s, 1 H), 7.52 (d, $J = 8$ Hz, 1 H), 7.42-7.38 (m, 3 H), 7.30-7.23 (m, 3 H), 7.03-6.97 (m, 1 H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 155.7, 140.5, 139.6, 129.9, 129.5, 129.1, 126.1, 123.9, 122.8, 120.5; IR (microscope) 3317, 1639, 1567, 1343 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{14}\text{BN}_2\text{O}_3$ ($\text{M}+\text{H}$)⁺ 257.1092, found 257.1093.

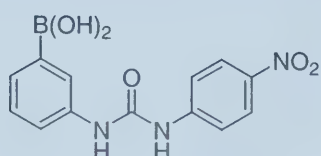
***N*-(4'-Methoxyphenylaminocarbonyl)-3-aminophenylboronic acid (64c).**



Beige solid (85% yield by mass; 78% yield by ^1H NMR with EtOAc int std): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.65 (s, 1 H), 7.50 (d, $J = 8$ Hz, 1H), 7.40-

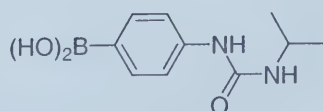
7.38 (m, 1 H), 7.32-7.22 (m, 3H), 6.89-6.84 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 157.3, 156.1, 139.7, 133.3, 129.4, 129.1, 126.0, 122.9, 122.7, 115.2, 56.0; IR (microscope) 3317, 3046, 2960, 1643, 1572, 1346 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{14}\text{H}_{16}\text{BN}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 287.1198, found 287.1197.

***N*-(4'-Nitrophenylaminocarbonyl)-3-aminophenylboronic acid (64d).**



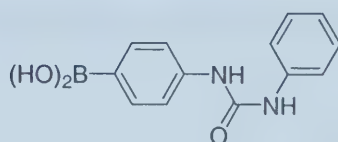
Bright yellow solid (85% yield by mass; 74% yield by ^1H NMR with EtOAc int std): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 8.20-8.15 (m, 2H), 7.68-7.63 (m, 3H), 7.55 (d, J = 8 Hz, 1H), 7.45-7.42 (m, 1H), 7.28 (t, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 154.6, 147.4, 143.4, 139.1, 130.0, 129.2, 126.2, 126.0, 122.9, 119.0; IR (microscope) 3365, 1705, 1552, 1329 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{13}\text{BN}_3\text{O}_5$ ($\text{M}+\text{H}$) $^+$ 302.0943, found 302.0943.

***N*-(*iso*-Propylaminocarbonyl)-4-aminophenylboronic acid (65a).**



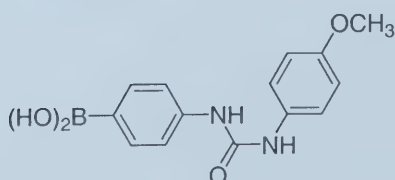
Cream solid (65% yield by mass): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.68-7.61 (m, 2H), 7.33-7.28 (m, 2H), 3.86 (h, $J = 7$ Hz, 1H), 1.15 (d, $J = 7$ Hz, 6H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 157.4, 143.0, 135.7, 127.7 (broad), 118.7, 42.8, 23.3; IR (microscope) 3327, 3045, 2973, 1650, 1595 cm^{-1} ; HRMS (ES, m/z) calcd $\text{C}_{10}\text{H}_{15}\text{BN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 245.1068, found 245.1075.

***N*-(Phenylaminocarbonyl)-4-aminophenylboronic acid (65b).**



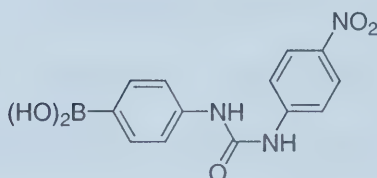
White solid (85% yield by mass): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.73-7.66 (m, 2H), 7.42-7.37 (m, 4H), 7.31-7.25 (m, 2H), 7.04-6.99 (m, 1H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 155.3, 142.4, 140.3, 135.8, 129.9, 128.1 (broad), 124.0, 120.5, 119.0; IR (microscope) 3391, 3313, 3057, 1671, 1591, 1531, 1499 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{14}\text{BN}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 257.1092, found 257.1092.

***N*-(4'-Methoxyphenylaminocarbonyl)-4-aminophenylboronic acid (65c).**

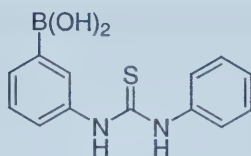


Cream solid (91% yield by mass; 84% yield by ^1H NMR with EtOAc int std): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.68-7.65 (m, 2H), 7.38-7.36 (m, 2H), 7.29 (d, $J = 9$ Hz, 2H), 6.86 (d, $J = 9$ Hz, 2H), 3.75 (s, 3H) ^{13}C NMR (75 MHz, 5% D_2O in THF-d_8) δ 156.0, 153.6, 143.1, 135.8, 134.2, 127.4 (broad), 120.8, 117.7, 114.6, 55.7; IR (microscope) 3390, 3305, 3051, 2961, 1662, 1589 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{14}\text{H}_{16}\text{BN}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 287.1198, found 287.1201.

***N*-(4'-Nitrophenylaminocarbonyl)-4-aminophenylboronic acid (65d).**



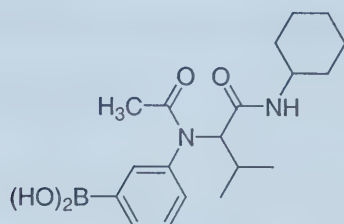
Bright yellow solid (92% yield by mass): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 8.16 (d, $J = 9$ Hz, 2H) 7.75-7.62 (m, 4H), 7.41 (d, $J = 8$ Hz, 2H); ^{13}C NMR (300 MHz, 5% D_2O in CD_3OD) δ 154.1, 147.2, 143.5, 141.9 (broad), 141.4 (broad), 135.7, 125.9, 119.3, 118.9; IR (microscope) 3439, 3354, 3303, 3109, 1724, 1621, 1598, 1574, 1546, 1521, 1498 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{13}\text{BN}_3\text{O}_5$ ($\text{M}+\text{H}$) $^+$ 302.0943, found 302.0940.

***N*-(Phenylaminothiocarbonyl)-3-aminophenylboronic acid (66).**

Resin **48** (100 mg, 0.0946 mmol, theor. loading: 0.946 mmol g⁻¹) was added to a 10 mL pp vessel and swollen in CH₂Cl₂ (2 mL). A solution of phenyl isothiocyanate (10% (v/v) in CH₃CN, 226 μL, 0.189 mmol) was added and the vessel was shaken for 20 h at rt. The suspension was drained, and the resin was rinsed with CH₂Cl₂ (5×). The product was then cleaved from the resin using the standard conditions described above. The combined filtrates were concentrated under reduced pressure and dried under high vacuum overnight to afford a cream colored solid (21 mg, 88% yield by mass; 82% yield by ¹H NMR with EtOAc int. std.): ¹H NMR (300 MHz, 5% D₂O in CD₃OD) δ 7.66 (s, 1H), 7.59 (d, *J* = 7 Hz, 1H), 7.47 (br d, *J* = 8 Hz, 1H), 7.41-7.32 (m, 5H), 7.23-7.17 (m, 1H); ¹³C NMR (75 MHz, 5% D₂O in CD₃OD) δ 181.9, 139.9, 139.2, 132.6, 131.5, 130.0, 129.3, 128.4, 127.1, 126.2; IR (microscope) 3214, 3054, 1597, 1530, 1497, 1429, 1344 cm⁻¹; HRMS (ES, *m/z*) calcd for C₁₃H₁₄BN₂O₂S (M+1)⁺ 273.0869, found 273.0871.

Multifunctional Boronic Acids

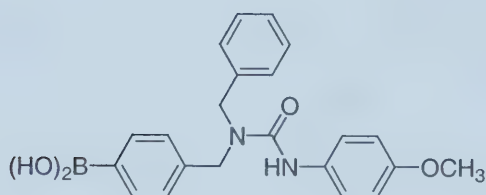
***N*-(Acetyl)-*N*-(1'-cyclohexylaminocarbonyl)-2'-methylpropane)-3-aminophenyl boronic acid (74).**



Resin **48** (122 mg, 0.115 mmol, theor. loading: 0.946 mmol g⁻¹) was added to a 10 mL pp vessel and swollen in THF (1 mL). Isobutyraldehyde (105 μ L, 1.150 mmol), glacial acetic acid (66 μ L, 1.150 mmol), and cyclohexylisocyanide (120 μ L, 1.150 mmol) were added in the given order and the vessel was shaken for 50 h at rt. The suspension was drained, and the resin was rinsed with THF (5 \times), CH₂Cl₂ (5 \times), and THF (5 \times). The product was then cleaved from the resin using the standard conditions described above. The product rinses were combined, concentrated under reduced pressure and dried under high vacuum overnight to afford a cream solid (26 mg, 67% yield by mass): ¹H NMR (300 MHz, 5% D₂O in CD₃OD)⁶⁹ δ 7.77 (d, *J* = 7 Hz, 1H), 7.59 (s, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 4.63 (d, *J* = 11 Hz, 1H), 3.62-3.54 (m, 1H), 2.17-2.04 (m, 1H), 1.90-1.83 (m, 1H), 1.78 (s, 3H); 1.78-1.69 (m, 3H), 1.63-1.51 (m, 1H), 1.41-1.13 (m, 5H); 1.04 (d, *J* = 7 Hz, 3H), 0.87 (d, *J* = 7 Hz, 3H); ¹³C NMR (125 MHz, 5% D₂O in CD₃OD) δ 174.3, 170.8, 140.9, 136.5 (broad), 135.8 (broad), 135.1, 132.0

(broad), 129.7, 68.4, 49.8, 33.5, 28.6, 26.6, 26.0, 23.5, 20.3, 19.9; IR (microscope) 3240, 3067, 2963, 2931, 1632, 1558 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{19}\text{H}_{29}\text{BN}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 383.2118, found 383.2111.

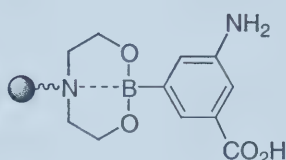
***N*-(Benzyl)-*N*-(4'-methoxyphenylaminocarbonyl)-4-aminomethylphenylboronic acid (75).**



In a 10 mL pp reaction vessel, resin **39** (180 mg, 0.0976 mmol, theor. loading: 0.542 mmol g^{-1}) was swollen in dry NMP (2 mL) and benzylamine (533 μL , 4.88 mmol) was added. The reaction vessel was shaken for 5 h, then drained and the resin was washed successively with dry DMF (3 \times), dry CH_2Cl_2 (5 \times), and dry THF (5 \times) and then dried overnight under high vacuum. This intermediate resin (151 mg, 0.0807 mmol, theor. loading: 0.534 mmol g^{-1}) was then swollen in CH_2Cl_2 (2 mL) and 4-methoxyphenylisocyanate (21 μL , 0.16 mmol) was added and the vessel was shaken for 5 h at rt. The suspension was drained, and the resin was rinsed with CH_2Cl_2 (8 \times). The product was then cleaved from the resin using the standard conditions described above. The combined filtrates were concentrated under reduced pressure and dried under high vacuum overnight to afford a yellow solid (67% yield by mass; 60% yield by ^1H NMR with EtOAc int. std.): ^1H

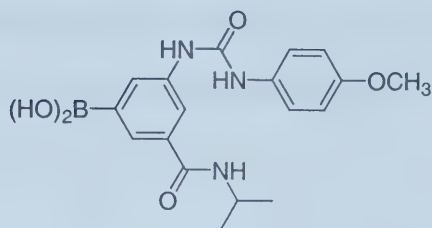
NMR (300 MHz, 5% D₂O in CD₃OD) δ 7.72 (d, J = 8 Hz, 2H), 7.36-7.28 (m, 3H), 7.26-7.16 (m, 6H), 6.83 (d, J = 9 Hz, 2H), 4.56 (s, 4H), 3.74 (s, 3H); ¹³C NMR (75 MHz, 5% D₂O in CD₃OD) δ 159.1, 157.7, 140.9, 138.8, 135.3, 133.3, 129.8, 128.5, 128.5, 127.6, 125.1, 114.9, 55.9, 50.7, 50.6; IR (microscope) 3327, 3030, 2932, 1638, 1610, 1512 cm⁻¹; HRMS (ES, m/z) calcd for C₂₂H₂₃BN₂O₄Na (M+Na)⁺ 413.1643, found 413.1631.

DEAM-PS supported 76.



This resin was prepared according to the general procedure for the immobilization of a boronic acid to DEAM-PS as described above but DMF was used as the immobilization solvent. Instead of being cleaved, this resin was dried under high vacuum for > 24 h.

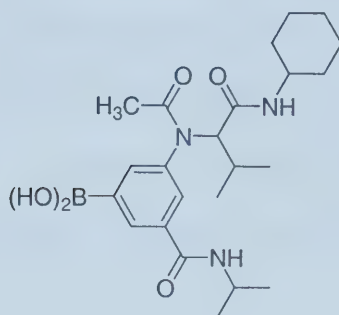
5-(*iso*-Propylaminocarbonyl)-*N*-(4'-methoxyphenylaminocarbonyl)-3-aminophenylboronic acid (77**).**



In a 10 mL pp reaction vessel, resin **76** (126 mg, 0.116 mmol, theor. loading: 0.923 mmol g⁻¹) was swollen in CH₂Cl₂ (2 mL) and 4-methoxyphenylisocyanate (30 μL, 0.23 mmol) was added and the vessel was shaken for 5 h at rt. The suspension was drained, and the resin was rinsed with CH₂Cl₂ (8×). Then the resin was swollen in NMP (2 mL). Isopropylamine (15 μL, 0.17 mmol), and PyBOP (91mg, 0.17 mmol) were added and the vessel was shaken for 26 h at rt. The suspension was drained, and the resin was rinsed with NMP (3×), THF (5×), and CH₂Cl₂ (6×). Cleavage of the resin-bound boronic acid using the standard conditions described above, followed by concentration of the filtrates afforded a yellow solid (77% yield by mass; 65% yield by ¹H NMR with EtOAc int. std.): ¹H NMR (300 MHz, 5% D₂O in CD₃OD)⁶⁹ δ 7.89 (br s, 1H), 7.80 (br s, 2H), 7.31 (d, *J* = 9 Hz, 2H), 6.88 (d, *J* = 9 Hz, 2H) 4.17 (h, *J* = 7 Hz, 1H), 3.76 (s, 3H), 1.24 (d, *J* = 7 Hz, 6H); ¹³C NMR (75 MHz, 5% D₂O in CD₃OD) δ 170.1, 157.3, 156.0, 140.0, 136.2, 133.0, 128.9, 128.0, 123.0, 121.2, 115.2, 56.1, 43.2, 22.6; IR (microscope)

3399, 3310, 2970, 1664, 1626, 1599, 1547, 1514 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{18}\text{H}_{22}\text{BN}_3\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$)⁺ 394.1550, found 394.1549.

***N*-(Acetyl)-*N*-(1'-cyclohexylaminocarbonyl-2'-methylpropane)-3-amino-5-(isopropylaminocarbonyl)phenylboronic acid (**78**).**

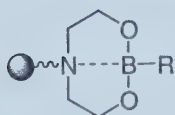


To resin **76** (139 mg, 0.128 mmol, theor. loading: 0.923 mmol g^{-1}) weighed out into a 10 mL pp reaction vessel was added NMP (2 mL). Isopropylamine (22 μL , 0.26 mmol), PyBOP (134 mg, 0.257 mmol) and DIPEA (89 μL , 0.51 mmol) were added and the vessel was shaken for 24 h at rt. The suspension was drained, and the resin was rinsed with NMP (3 \times), CH_2Cl_2 (3 \times) and THF (5 \times) and then swollen in THF (2 mL). Isobutyraldehyde (116 μL , 1.28 mmol), glacial acetic acid (73 μL , 1.3 mmol) and cyclohexylisocyanide (134 μL , 1.28 mmol) were added in the given order and the vessel was shaken for 49 h at rt. The suspension was drained, and the resin was rinsed with THF (5 \times), CH_2Cl_2 (5 \times), and THF (5 \times). The product was then cleaved from the resin using the standard conditions described above. The product rinses were combined, concentrated under reduced

pressure and dried under high vacuum overnight to afford a white solid (53% yield by mass; 42% yield by ^1H NMR with EtOAc int. std.): ^1H NMR (500 MHz, 5% D_2O in CD_3OD)⁶⁹ δ 8.17 (s, 1H), 7.74 (s, 1H) 7.68 (s, 1H), 4.72 (d, J = 11 Hz, 1H), 4.19 (h, J = 7 Hz, 1H), 3.62-3.48 (m, 1H), 2.11-2.06 (m, 1H), 1.88-1.85 (m, 1H), 1.80 (s, 3H), 1.78-1.70 (m, 3H), 1.62-1.60 (m, 1H), 1.38-1.15 (m, 11H), 1.06 (d, J = 7 Hz, 3H) 0.88 (d, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 174.1, 170.6, 169.0, 143.5, 141.0 (broad), 136.8, 133.6, 131.1 (broad), 68.9, 67.9, 43.3, 33.5, 33.5, 28.7, 26.5, 26.4, 26.0, 26.0, 23.6, 22.5, 20.2, 19.8; IR (microscope) 3308, 2969, 2932, 2856, 1640, 1586, 1537, 1428 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{23}\text{H}_{37}\text{BN}_3\text{O}_5$ ($\text{M}+\text{H}$)⁺ 446.2821, found 446.2816.

Resin-to-Resin Transfer Reactions

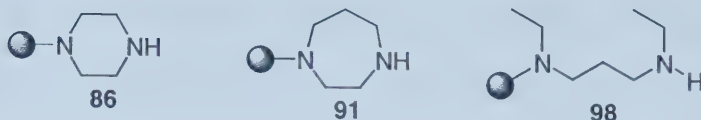
DEAM-PS supported 11a-f.



- a R=2-Me-C₆H₄
- b R=4-MeO-C₆H₄
- c R=4-Br-C₆H₄
- d R=1-Naphthyl
- e R=*E*-HC=CH(Bu)
- f R=2,6-F₂-C₆H₄

These resins were prepared according to the general procedures for the immobilization of resin-bound boronic acids as described above. Instead of being cleaved, the resins were dried under high vacuum for > 24 h.

Typical preparation for the dialkylaminotrityl resins **86**, **91** and **98**.

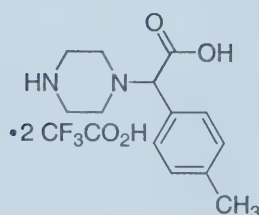


Preparation of 86. Trityl chloride resin (500 mg, 0.535 mmol, theor. loading: 1.07 mmol g⁻¹) was weighed into a 70 ml pp vessel and a solution of piperazine (920 mg, 10.7 mmol) in NMP (20 mL) was added. The reaction was shaken at rt overnight. The suspension was drained, and the resin was rinsed with MeOH (3×), and CH₂Cl₂ (6×). The resin was dried under high vacuum for > 24 h to afford a yellow resin (460 mg, theor. 515 mg, 1.02 mmol g⁻¹).

Typical procedure for the borono-Mannich RRTR: Preparation of 94b. To piperazinetrityl resin **86** (32 mg, 0.030 mmol, theor. loading: 0.95 mmol g⁻¹) weighed out in a 10 ml teflon fritted reaction vessel was added a solution of glyoxylic acid monohydrate (0.032 mmol) in dry THF (2 mL). The suspension was allowed to mix at rt under a nitrogen atmosphere for 2 h. An excess of DEAM-PS boronic ester **11b** (127 mg, 0.120 mmol, theor. loading: 0.950 mm g⁻¹) was then added, followed by a 8:3 THF/EtOH solution (1.5 mL). The suspension was mixed at 65°C for 48 h under a nitrogen atmosphere and then cooled to rt. The resin mixture was filtered and rinsed with 8:3 THF/EtOH (3×), 2:1 THF/H₂O (3×) and CH₂Cl₂ (5×), mixed with 3 ml of 5% TFA/CH₂Cl₂ in the same vessel at rt for 1 h, then filtered and rinsed with CH₂Cl₂ (3×) and MeOH (2×). The combined

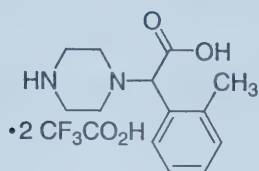
filtrates were concentrated and dried under high vacuum for 12 h to afford crude **94b** as a clear oil (14 mg, 90% conversion). An analytically pure sample was obtained by dissolving the oil in a small amount of methanol followed by addition of ether, filtration of the precipitate, and concentration of the resulting solution. See characterization below.

Piperazin-1-yl-*p*-tolyl-acetic acid bis(trifluoroacetic acid) salt (88).



^1H NMR (300 MHz, CD_3OD) δ 7.30 (d, $J = 8$ Hz, 2H), 7.20 (d, $J = 8$ Hz, 2H), 4.17 (s, 1H), 3.23-3.20 (m, 4H), 2.77-2.74 (m, 4H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.5, 140.5, 132.0, 130.7, 130.1, 73.3, 48.1, 44.3, 21.2; IR (MeOH cast) 3380, 3200-2500, 1674, 1426 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 235.1447, found 235.1444.

Piperazin-1-yl-*o*-tolyl-acetic acid bis(trifluoroacetic acid) salt (94a).



^1H NMR (300 MHz, CD_3OD) δ 7.40 (d, $J = 6$ Hz, 1H), 7.24-7.18 (m, 3H), 4.50 (s, 1H), 3.20-3.16 (m, 4H), 2.85-2.82 (m, 4H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.2, 138.9, 134.7, 131.8, 129.3, 129.1, 127.1, 69.3, 47.7, 44.9, 19.4; IR (MeOH cast) 3412, 3200-2400, 1675, 1428 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 235.1447, found 235.1448.

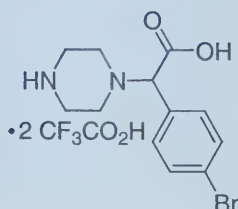
(4-Methoxy-phenyl)-piperazin-1-yl-acetic acid bis(trifluoroacetic acid) salt (94b).



^1H NMR (300MHz, CD_3OD) δ 7.34 (d, $J = 9$ Hz, 2H), 6.93 (d, $J = 9$ Hz, 2H), 4.13 (s, 1H), 3.79 (s, 3H), 3.23-3.19 (m, 4H), 2.75-2.72 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.3, 161.7, 131.2, 127.9, 115.2, 73.1, 55.7, 48.3, 44.7; IR (MeOH

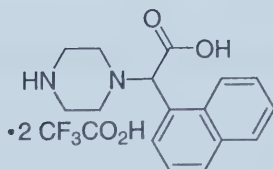
cast) 3350, 3200-2400, 1685, 1611 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$)⁺ 251.1396, found 251.1393.

(4-Bromo-phenyl)-piperazin-1-yl-acetic acid bis(trifluoroacetic acid) salt (94c).



^1H NMR (300 MHz, CD_3OD) δ 7.55 (d, $J = 9$ Hz, 2H), 7.36 (d, $J = 9$ Hz, 2H), 4.22 (s, 1H), 3.25-3.19 (m, 4H), 2.77-2.73 (m, 4H); LRMS (ES, m/z) 301.1 ($\text{M}+\text{H}$)⁺.

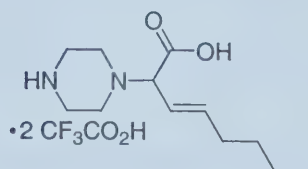
Naphthalen-2-yl-piperazin-1-yl-acetic acid bis(trifluoroacetic acid) salt (94d).



^1H NMR (300 MHz, CD_3OD) δ 8.43 (d, $J = 8$ Hz, 1H) 7.91-7.88 (m, 2H), 7.60-7.45 (m, 4H), 5.06 (s, 1H) 3.16-3.12 (m, 4H), 2.93-2.90 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.3, 135.7, 133.4, 132.4, 130.5, 129.8, 128.4, 127.6, 127.1, 126.2,

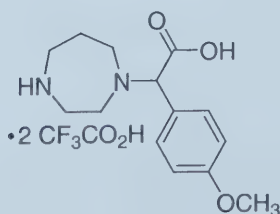
125.2, 70.1, 47.9, 45.2; IR (MeOH cast) 3200-2400, 1675, 1431 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$)⁺ 271.1447, found 271.1452.

***E*-2-Piperazin-1-yl-oct-3-enoic acid bis(trifluoroacetic acid) salt (94e).**



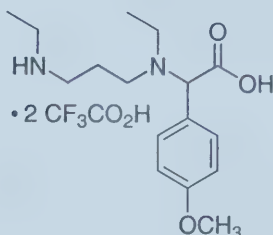
^1H NMR (300 MHz, CD_3OD) δ 5.89 (dt, $J_1 = 15$ Hz, $J_2 = 7$ Hz, 1H) 5.48 (dd, $J_1 = 15$ Hz, $J_2 = 8$ Hz, 1H) 3.70 (d, $J = 8$ Hz, 1H) 3.26-3.23 (m, 4H), 2.95-2.87 (m, 2H), 2.84-2.76 (m, 2H), 2.12 (app q, $J = 7$ Hz, 2H) 1.44-1.29 (m, 4H) 0.92 (t, $J = 7$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.9, 140.5, 124.3, 71.8, 48.1, 44.6, 33.2, 32.2, 23.2, 14.2; IR (MeOH cast) 3200-2400, 1673, 1427 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{12}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$)⁺ 227.1760, found 227.1759.

(4-Methoxyphenyl)-homopiperazin-1-yl-acetic acid bis(trifluoroacetic acid) salt (95b).



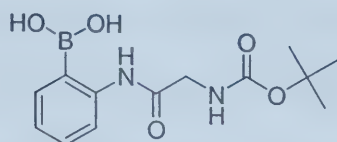
^1H NMR (300 MHz, CD_3OD) δ 7.38 (d, $J = 9$ Hz, 2H), 6.96 (d, $J = 9$ Hz, 2H), 4.65 (s, 1H), 3.80 (s, 3H), 3.34-3.21 (m, 2H) 3.21- 3.10 (m, 4H), 3.01-2.97 (m, 2H), 2.07-2.04 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.4, 161.8, 131.5, 128.0, 115.4, 73.1, 55.8, 53.3, 49.2, 46.7, 45.9, 26.1; IR (MeOH cast) 3417, 3200-2400, 1678, 1516 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 265.1547, found 265.1544.

[Ethyl-(3-ethylamino-propyl)-amino]-(4-methoxy-phenyl)-acetic acid bis(trifluoroacetic acid) salt (99b).



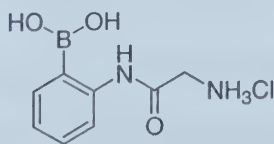
^1H NMR (300 MHz, CD_3OD) δ 7.48 (d, $J = 9$ Hz, 2H), 7.03 (d, $J = 9$ Hz, 2H), 5.16 (s, 1H), 3.83 (s, 3H), 3.40-3.22 (m, 2H), 3.12-2.95 (m, 6H), 2.19-2.01 (m, 2H), 1.32-1.26 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 163.1, 132.3, 122.2, 116.2, 70.2, 56.0, 49.4, 48.0, 45.2, 44.2, 22.2, 11.4, 8.8; IR (MeOH cast) 3400, 3200-2500, 1675, 1612 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 295.2016, found 295.2013.

***N*-[*N*-(*tert*-Butyloxycarbonyl)-glycyl]-2-aminophenylboronic acid (**123**).**



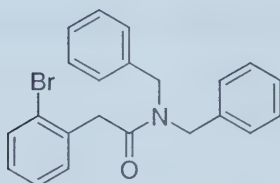
To a solution of *t*-Boc-Gly-OH (117 mg, 0.670 mmol) in THF (5 mL) was added *ortho*-aminophenylboronic acid (91 mg, 0.67 mmol) followed by DCC (138 mg, 0.670 mmol). This mixture containing a white precipitate was stirred at rt for 5 h. The reaction was then filtered and the filtrate was concentrated under reduced pressure to yield an oil which was purified using flash chromatography (1:19:80 AcOH/MeOH/CH₂Cl₂) to furnish **123** as a white solid (135 mg, 69%): ¹H NMR (300 MHz, CD₃OD) δ 7.44 (m, 1H), 7.27 (m, 2H), 7.09 (m, 1H), 4.11 (s, 2H), 1.46(s, 9H); ¹³C NMR (75 MHz, CD₃OD) δ 172.3, 158.4, 138.9, 133.1, 129.1, 127.9, 117.1, 81.1, 43.8, 28.7; IR (microscope) 3600-2400, 3283, 3061, 2978, 1697, 1638, 1607 cm⁻¹; HRMS (ES, m/z) calcd for C₁₃H₁₈BN₂O₄ ((M-H₂O) + H)⁺ 277.1360, found 277.1362.

2-(2-Amino-acetyl-amino)-phenylboronic acid hydrochloride salt (124**).**



Boronic acid **123** (344 mg, 1.17 mmol) was stirred in 4.0 M HCl/dioxane (10 mL) at rt for 4 h. This mixture was concentrated under reduced pressure to yield a crude solid. The solid was triturated with CH₂Cl₂, filtered and the cream crystals were dried under vacuum overnight to yield **124** (269 mg, 99%): ¹H NMR (300 MHz, CD₃OD) δ 7.44 (m, 1H), 7.32 (m, 2H), 7.14 (m, 1H), 4.24 (s, 2H); ¹³C NMR (75 MHz, CD₃OD) δ 167.2, 138.4, 133.2, 129.7, 128.2, 117.9, 41.2; IR (microscope) 3500-2000, 1646, 1609, 1565 cm⁻¹; HRMS (ES, m/z) calcd for C₈H₁₀BN₂O₂ ((M-H₂O) + H)⁺ 177.0835, found 177.0842.

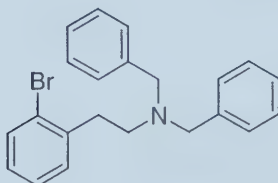
***N,N*-Dibenzyl-2-(2-bromo-phenyl)-acetamide (130).**



2-Bromophenylacetic acid **129** (5.00 g, 23.3 mmol) was weighed into a 10 mL round bottom flask and thionyl chloride (8.50 mL, 117 mmol) was added. A reflux condenser was attached and the solution was refluxed at 80 °C for 4 h. Upon cooling, the excess thionyl chloride was removed under reduced pressure. The resulting residue was dissolved in toluene (30 mL) and dibenzylamine (11.2 mL, 58.3 mmol) was added when a thick white precipitate was deposited. This mixture was stirred at rt for 2 h and water was then added. The pasty precipitate was filtered through a fritted funnel rinsing with both water and toluene. The

resulting filtrate was then transferred to a separatory funnel and the layers were separated. The organic layer was washed with 1 N aqueous HCl, dried with anhydrous MgSO_4 , filtered and concentrated under reduced pressure to yield a yellow oil. This oil was purified by flash chromatography (30% EtOAc in hexanes) to furnish **130** as a yellow solid (4.95 g, 54%): ^1H NMR (300 MHz, CD_3OD) δ 7.54 (d, $J = 8$ Hz, 1H), 7.38-7.21 (m, 12H), 7.17-7.11 (m, 1H), 4.60 (s, 4H), 3.94 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.9, 138.4, 137.7, 136.8, 133.7, 132.8, 130.0, 129.9, 129.6, 129.3, 128.7, 128.7, 128.5, 127.9, 126.1, 51.7, 50.0, 41.9; IR (CH_2Cl_2 cast) 3062, 3029, 2922, 1652, 1604 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{22}\text{H}_{20}\text{NOBrNa}$ ($\text{M}+\text{Na}$) $^+$ 416.0626, found 416.0623.

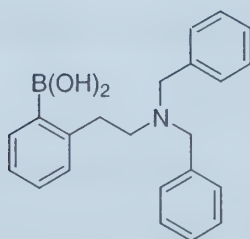
***N,N*-Dibenzyl-[2-(2-bromo-phenyl)- ethyl]-amine (131).**



A solution of **130** (2.12 g, 5.38 mmol) in THF (42 mL) was added at 0 °C to a 1 M borane-THF complex solution (27.4 mL, 27.4 mmol) and the reaction was stirred at reflux for 22 h. Upon cooling, methanol (28 mL) and 10% potassium hydroxide (9 mL) was added. This mixture was then stirred at reflux for a further 2 h. The solution was concentrated under reduced pressure, diluted with chloroform and washed with saturated aqueous NaCl. The organic layer was separated, dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to furnish **131** as a clear oil (1.61 g, 79%): ^1H NMR (300 MHz, CDCl_3) δ 7.45-7.43 (m, 1H), 7.33-7.13 (m, 11H), 7.08-7.06 (m, 1H), 7.03-6.97 (m, 1H), 3.66 (s, 4H), 2.95-2.90 (m, 2H), 2.71-2.66 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.8, 139.6, 132.6, 130.9, 128.6, 128.1, 127.5, 127.2, 126.7, 124.5, 58.3, 53.4, 33.9; IR (CHCl_3 cast) 3061, 3026, 2932, 2797, 1601, 1566, 1494 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{22}\text{H}_{23}\text{NBr}$ ($\text{M}+\text{H}$) $^+$ 380.1014, found 380.1008; Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{NBr}$: C, 69.48; H, 5.83; N, 3.68; Br, 21.01. Found: C, 69.80; H, 5.78; N, 3.73; Br, 20.76.

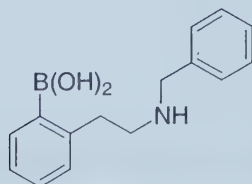
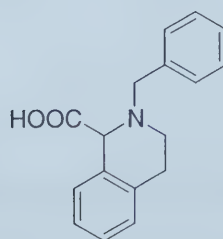
2-(2-Dibenzylamino-ethyl)-phenylboronic acid (**132**).



A solution of distilled bromide **131** (198 mg, 0.521 mmol) in THF (4 mL) was placed at $-78\text{ }^\circ\text{C}$ and a 1.6 M solution of *n*-butyllithium (651 μL , 1.04 mmol) was added. The resulting solution was stirred at $0\text{ }^\circ\text{C}$ for 1 h. Triisopropylborate (240 μL , 1.04 mmol) was added at $0\text{ }^\circ\text{C}$ and then the reaction was stirred at rt for 5 h. The solution was quenched with water (2 mL) and the organic solvents were removed under reduced pressure. The aqueous mixture was then extracted with

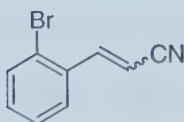
EtOAc (5×). The combined organic layers were dried with anhydrous MgSO_4 , filtered and concentrated under reduced pressure to yield a clear yellow oil. This residue was dried under high vacuum for 2 h and then dissolved in THF (8 mL) and vortexed with DEAM-PS **10** (500 mg, 0.533 mmol, theor. loading: 1.07 mmol g^{-1}) in a 20 mL pp reaction vessel for 1 h. The product was then cleaved from the resin using the standard conditions described above. The product rinses were combined, concentrated under reduced pressure to give **132** as a white solid (20 mg, 12%): ^1H NMR (500 MHz, CD_3OD) δ 7.35 (br m, 1H), 7.32-7.31 (m, 4H), 7.29-7.26 (m, 4H), 7.22-7.18 (m, 3H), 7.10 (t, $J = 7$ Hz, 1H), 7.01 (d, $J = 8$ Hz, 1H), 3.60 (s, 4H), 2.90-2.87 (m, 2H), 2.65-2.62 (m, 2H); ^{13}C NMR (300 MHz, 5% D_2O in CD_3OD) δ 145.2, 140.2, 133.7, 130.2, 130.2, 129.9, 129.5, 129.2, 128.0, 126.2, 59.4, 56.9, 34.6; IR (microscope) 3348, 3085, 292, 1597, 1494 cm^{-1} ; HRMS (ES, m/z) calcd for $\text{C}_{22}\text{H}_{25}\text{BNO}_2$ ($\text{M}+\text{H}$) $^+$ 346.1973, found 346.1974.

Preliminary results on the preparation of 2-(2-Benzylamino-ethyl)-phenylboronic acid (133) and 2-Benzyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid (134).

**133****134**

To a solution of boronic acid **132** (14 mg, 0.041 mmol) in 100% EtOH (1 mL) was added 10% Pd/C (9 mg, 0.008 mmol) in portions. The resulting black suspension was degassed and then stirred under a hydrogen atmosphere via a hydrogen balloon set-up for 16 h at rt and atmospheric pressure. The suspension was then filter through celite and the filtrate was concentrated under reduced pressure to yield crude **133** (8 mg): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.48-7.36 (m, 4H), 7.32-7.20 (m, 1H), 7.12-7.02 (m, 2H), 7.02-6.92 (m, 1H), 3.92 (s, 2H), 3.16-3.00 (m, 2H), 2.92-2.82 (m, 2H); LRMS (ES, m/z) 256.1 ($\text{M}+\text{H}$) $^+$. This crude oil was then dissolved in 100% EtOH (1 mL) and glyoxylic acid monohydrate (3 mg, 0.03 mmol) was added. The reaction was stirred at rt for 16 h. A 25 μL aliquot was taken for ES-MS analysis. The reaction was then refluxed for 5 h at 80 $^\circ\text{C}$. Upon cooling, the solvent was removed under reduced pressure to yield known⁷⁰ **134** as a crude oil.

3-(2-Bromo-phenyl)-acrylonitrile (**139**).



A mixture of (triphenylphosphoranylidene)-acetonitrile (392 mg, 1.30 mmol) in THF (4 mL) was cooled to -78 $^\circ\text{C}$ and treated with a solution of *ortho*-bromobenzaldehyde (117 μL , 1.00 mmol) in THF (1 mL). The resultant solution was allowed to warm to rt over 2 h and then stirred for 16 h. The reaction was

quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 \times). The combined organic layers were washed with water, saturated aqueous NaCl , dried with anhydrous MgSO_4 , filtered and concentrated under reduced pressure to furnish crude **139** as a 1:2.5 ratio of trans:cis isomers. The clear oil/white solid was purified by flash chromatography (15% EtOAc in hexanes) to give a mixture of both the *E* and *Z* isomers of **139** (159 mg, 77%). Partial separation of the two isomers allowed for their characterization separately.

(E)-139: ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, $J = 17$ Hz, 1H), 7.61 (d, $J = 8$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 1H), 7.34 (t, $J = 8$ Hz, 1H), 7.27 (t, $J = 8$ Hz, 1H), 5.84 (d, $J = 17$ Hz, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 149.0, 133.6, 133.5, 132.1, 127.9, 127.0, 124.7, 117.5, 99.1; IR (CHCl_3 cast) 3061, 2219, 1615, 1586 cm^{-1} ; HRMS (EI, m/z) calcd for $\text{C}_9\text{H}_6\text{N}^{81}\text{Br}$ (M) $^+$ 208.9663, found 208.9661 and calcd for $\text{C}_9\text{H}_6\text{N}^{79}\text{Br}$ (M) $^+$ 206.9684, found 206.9680.

(Z)-139: ^1H NMR (500 MHz, CDCl_3) 70 δ 8.00 (dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz, 1H), 7.62 (dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz, 1H), 7.48 (d, $J = 12$ Hz, 1H), 7.39 (m, 1H), 7.28 (app dt, $J_1 = 2$ Hz, $J_2 = 8$ Hz, 1H), 5.57 (d, $J = 12$ Hz, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 147.8, 133.4, 133.1, 131.8, 129.2, 127.8, 124.5, 116.4, 98.3; IR (CHCl_3 cast) 3061, 2218, 1613, 1588 cm^{-1} ; HRMS (EI, m/z) calcd for $\text{C}_9\text{H}_6\text{N}^{81}\text{Br}$ (M) $^+$ 208.9663, found 208.9660 and calcd for $\text{C}_9\text{H}_6\text{N}^{79}\text{Br}$ (M) $^+$ 206.9684, found 206.9679.

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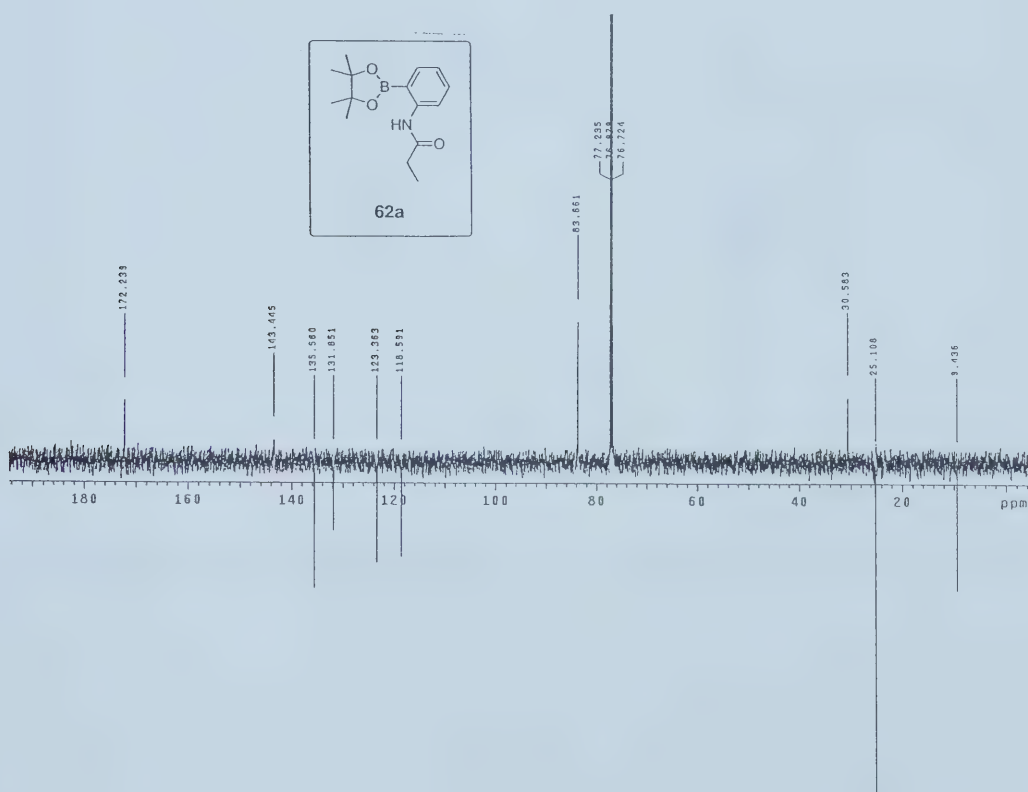
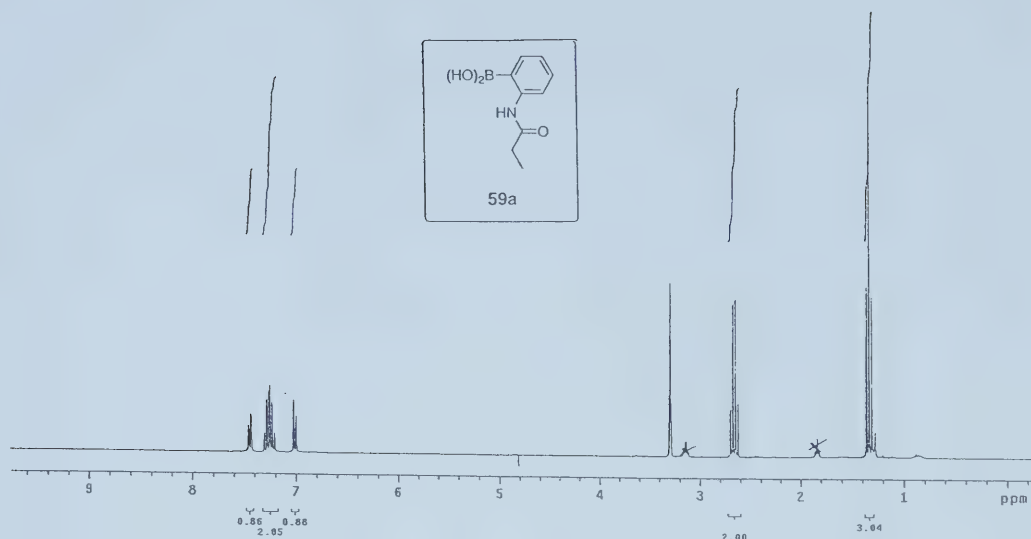
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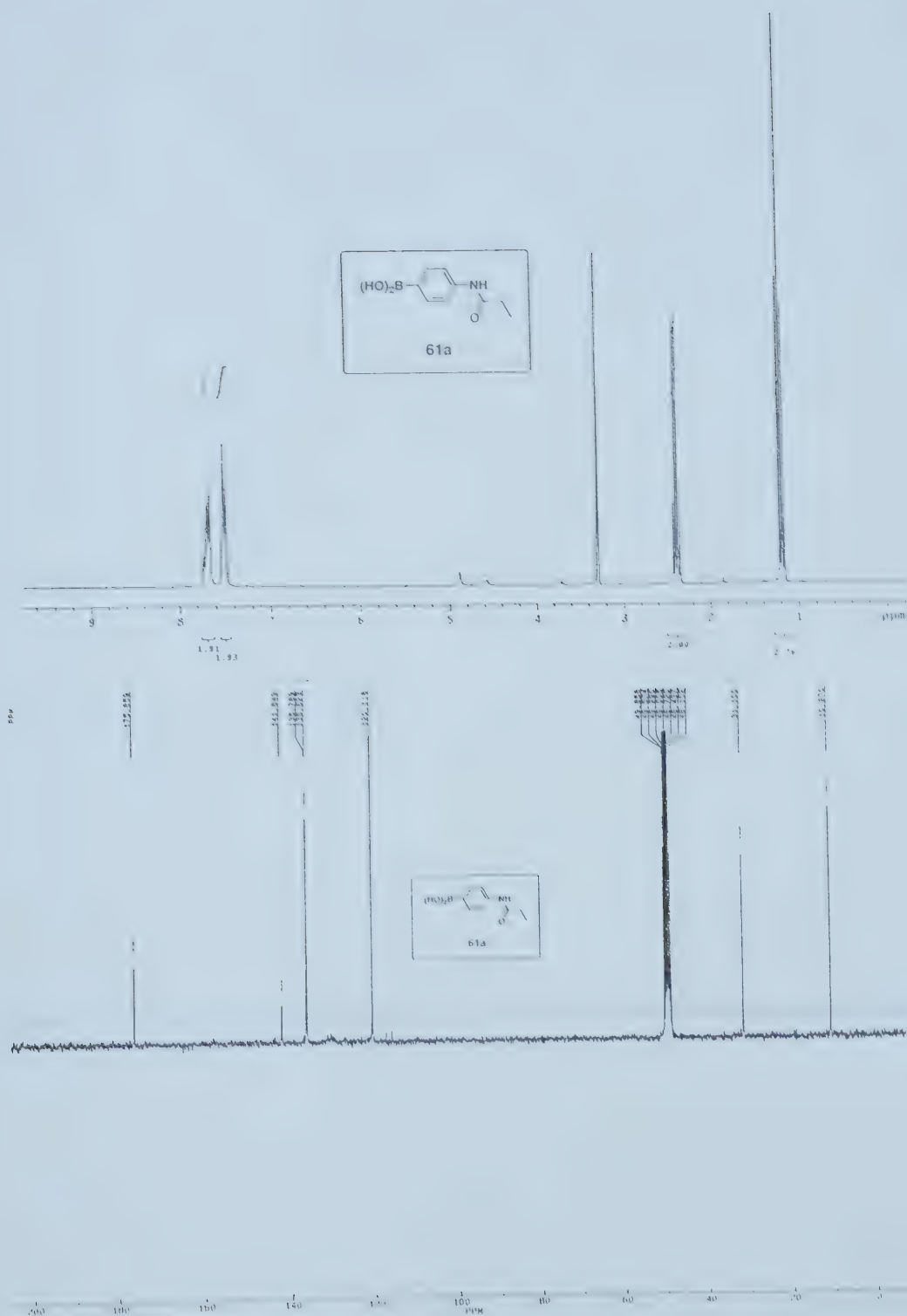
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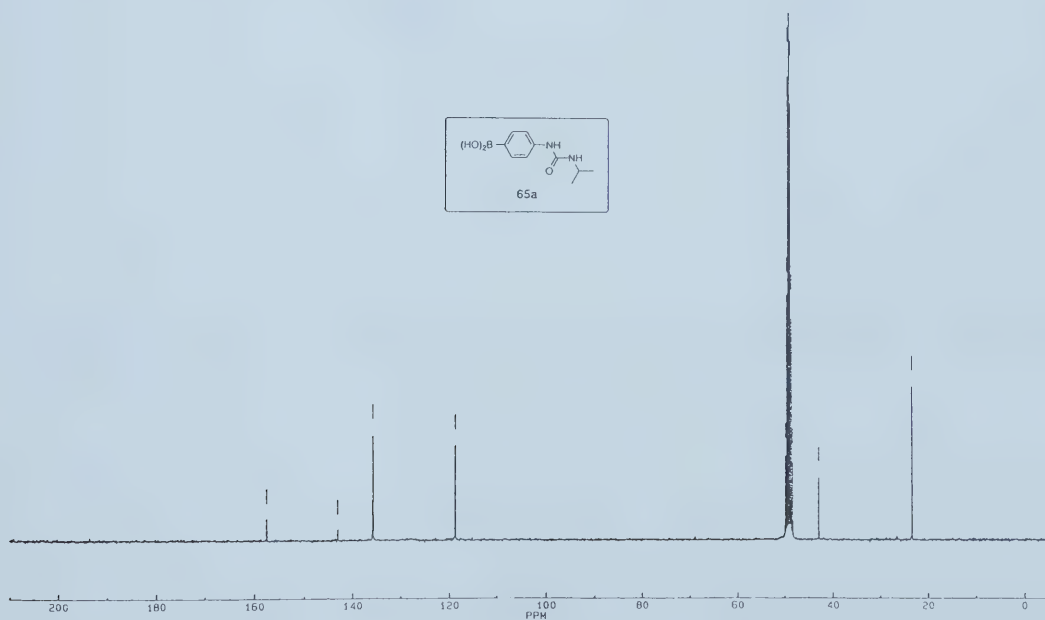
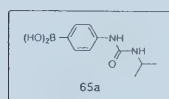
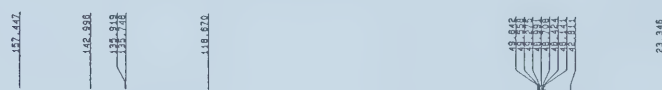
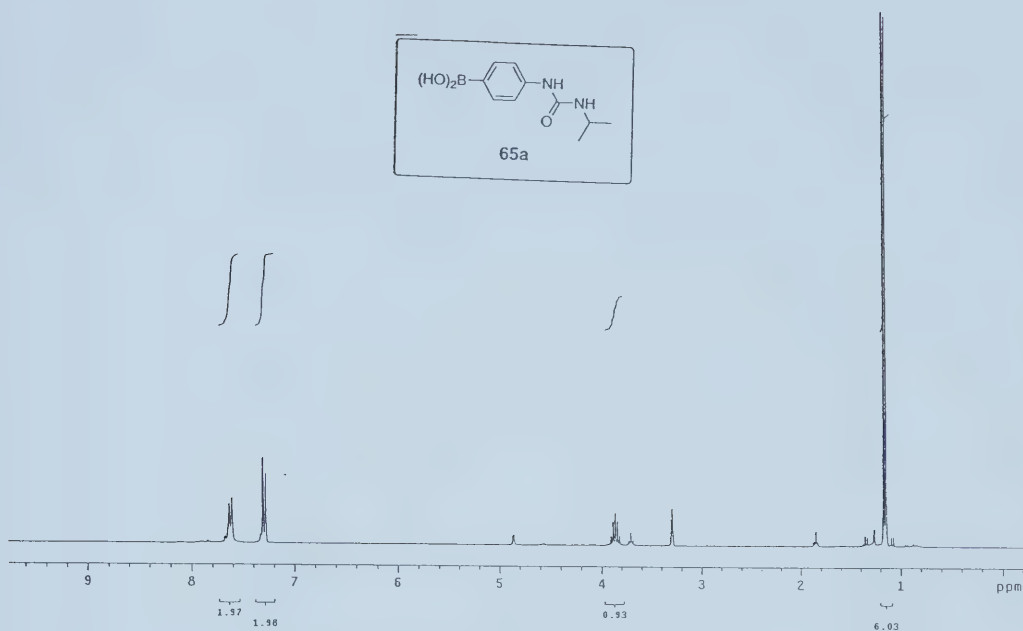
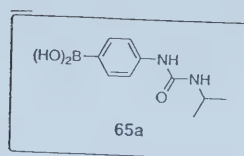
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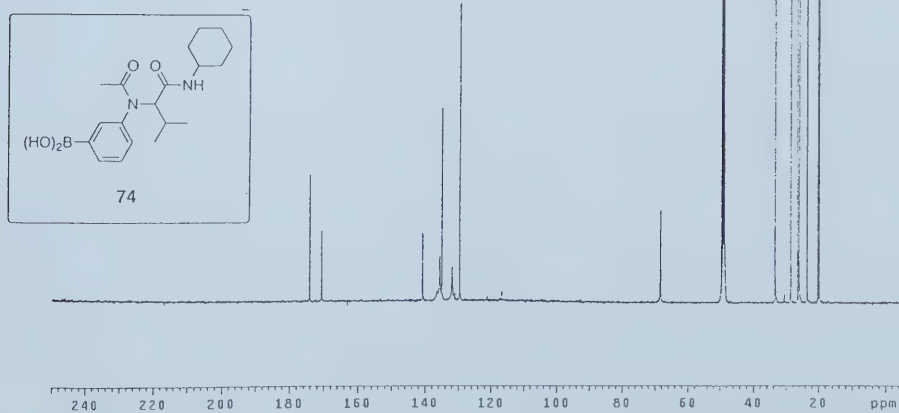
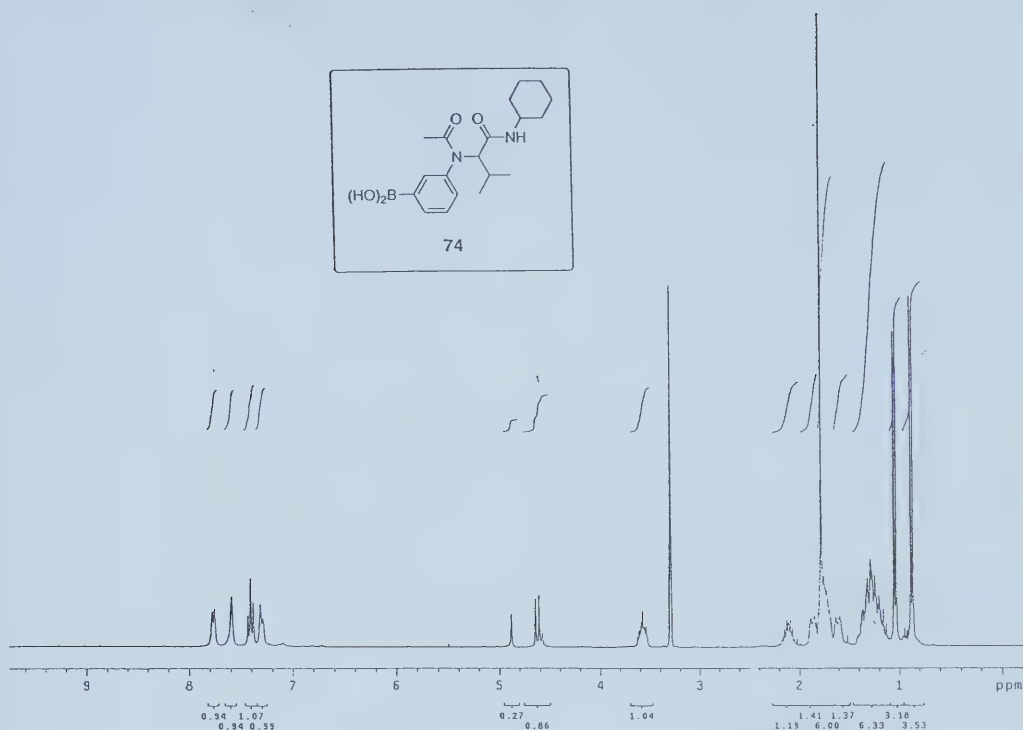
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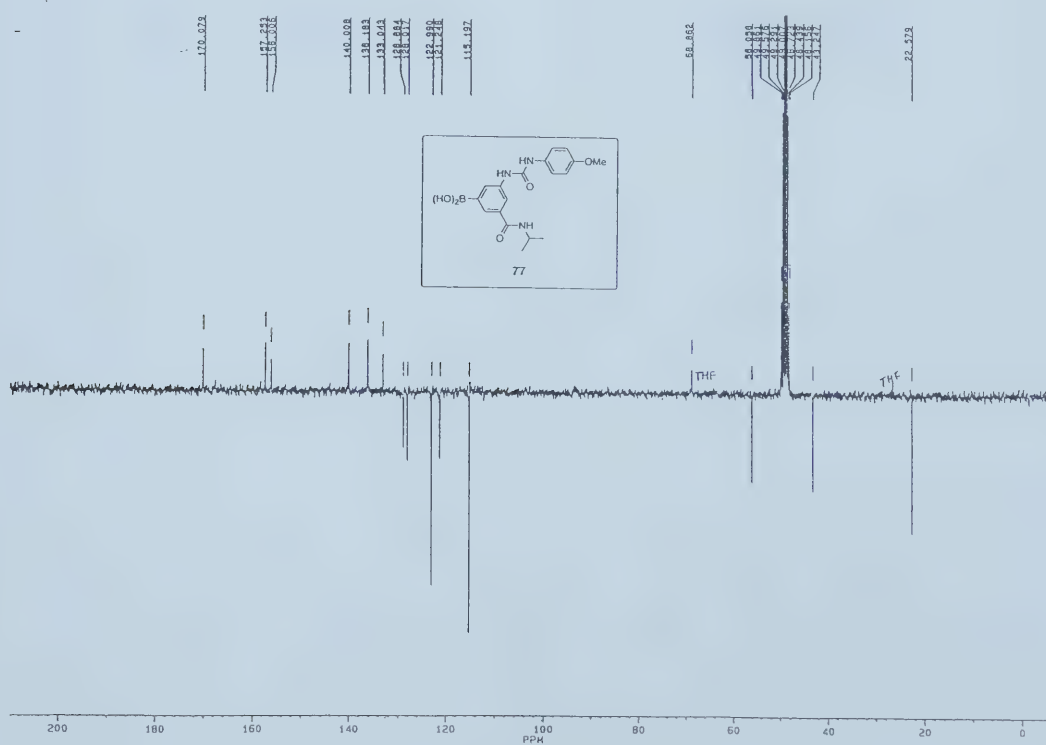
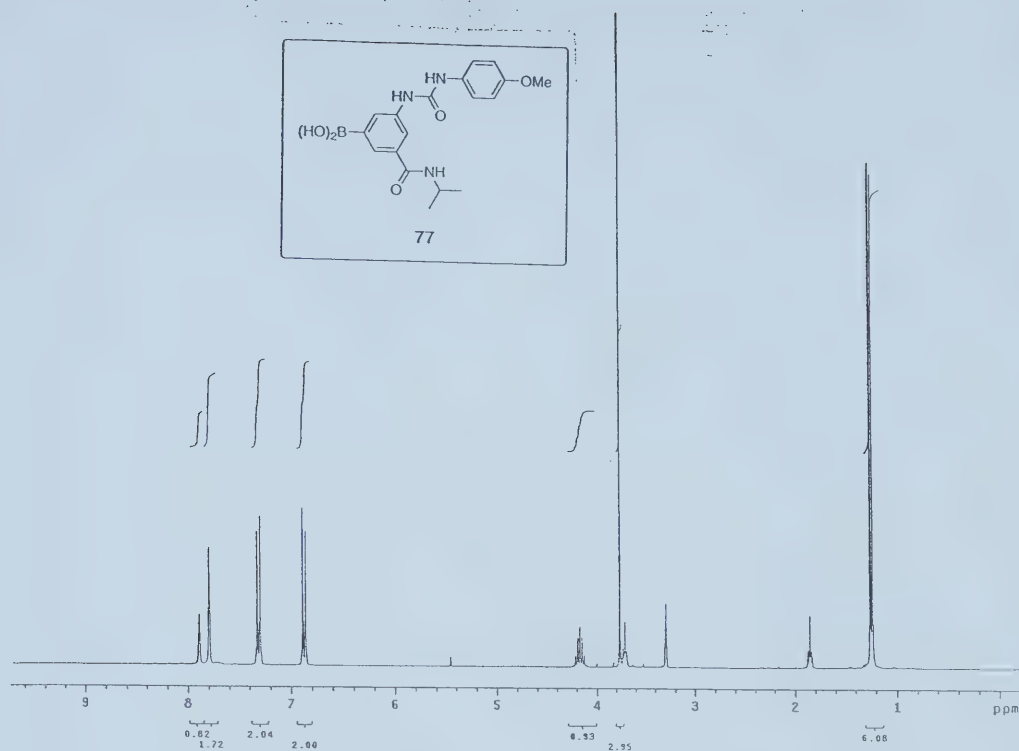


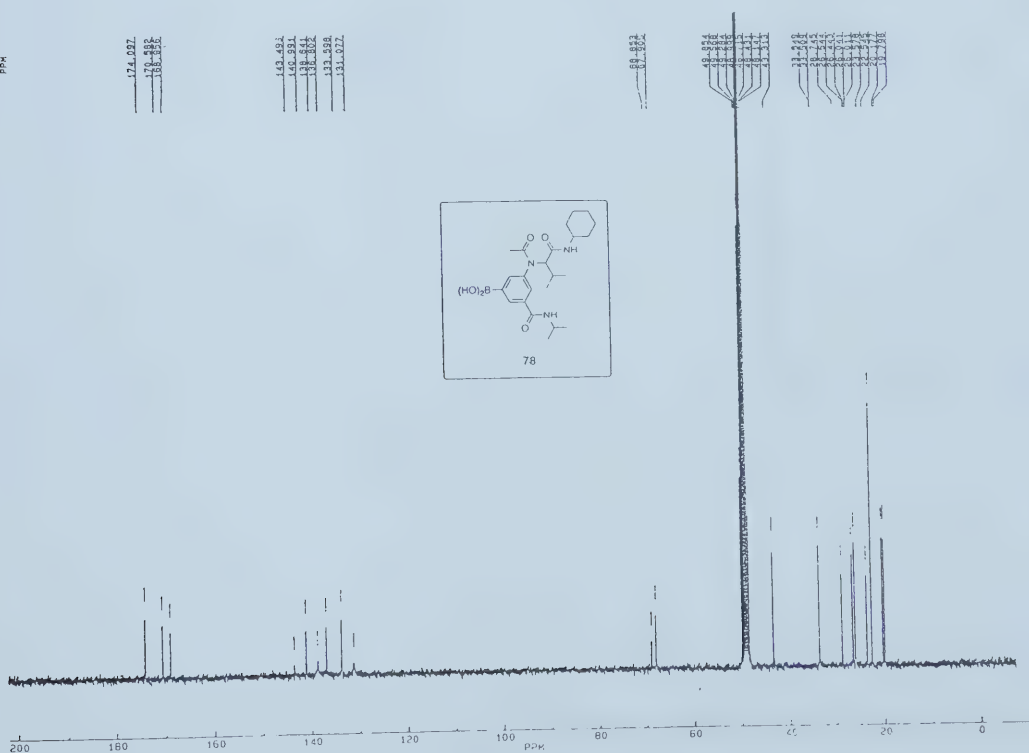
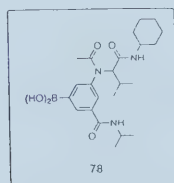
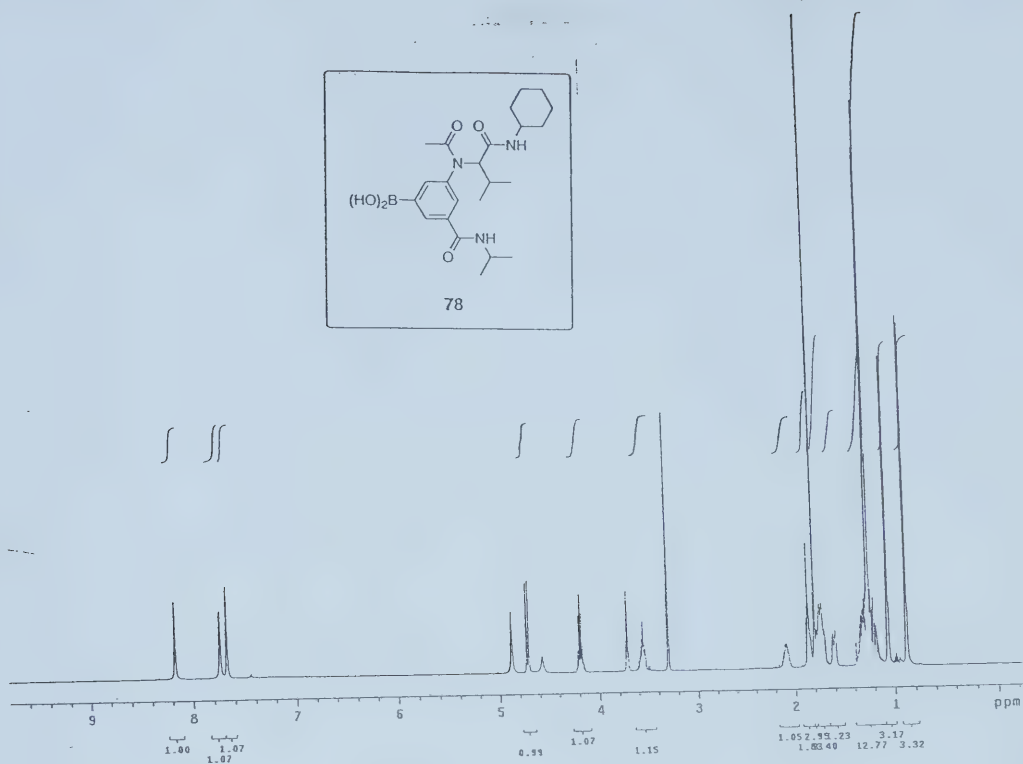
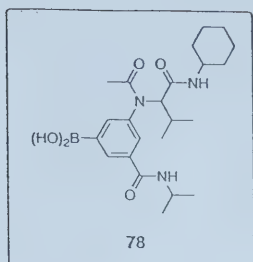


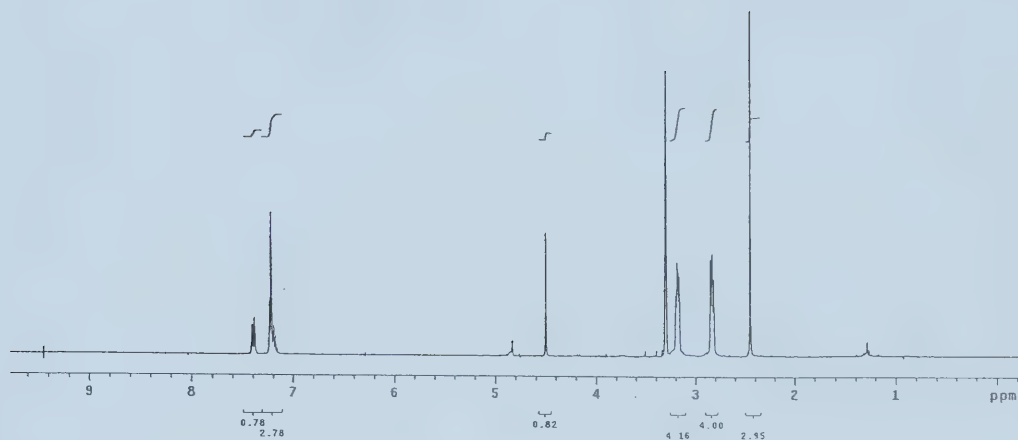
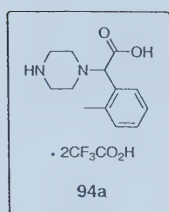


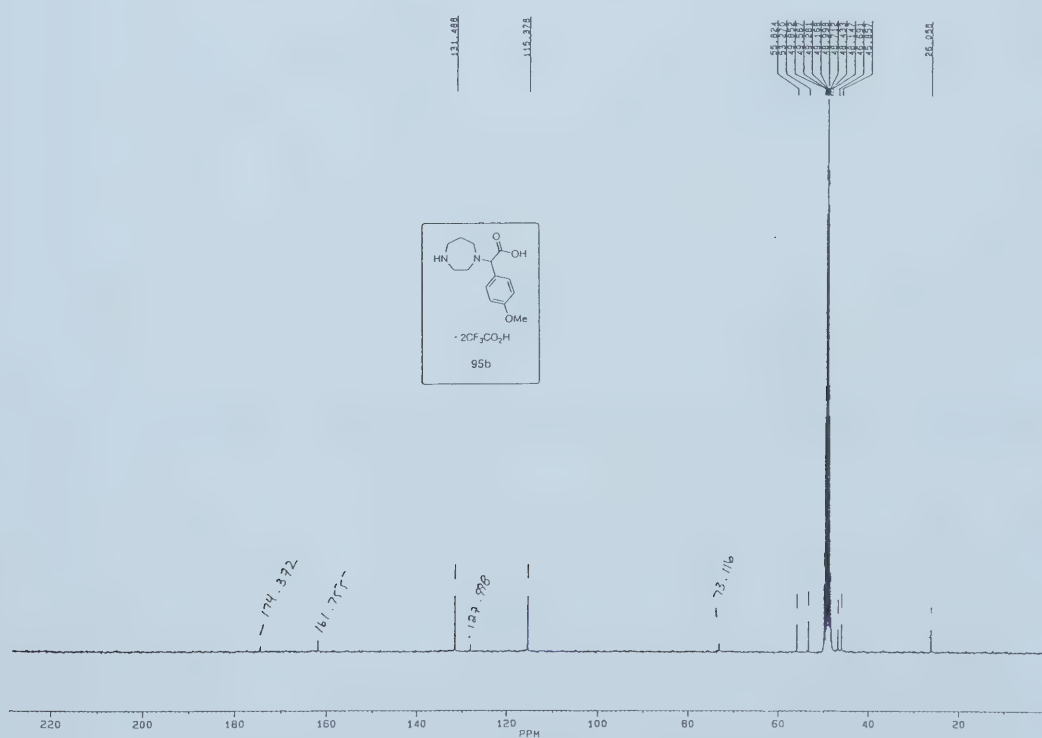
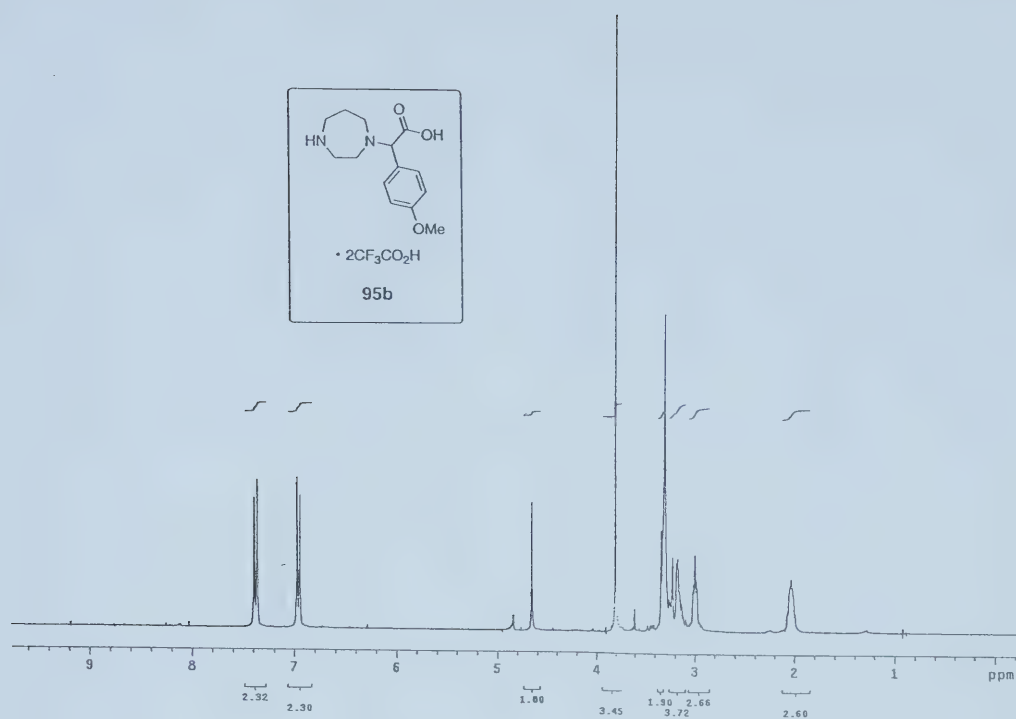


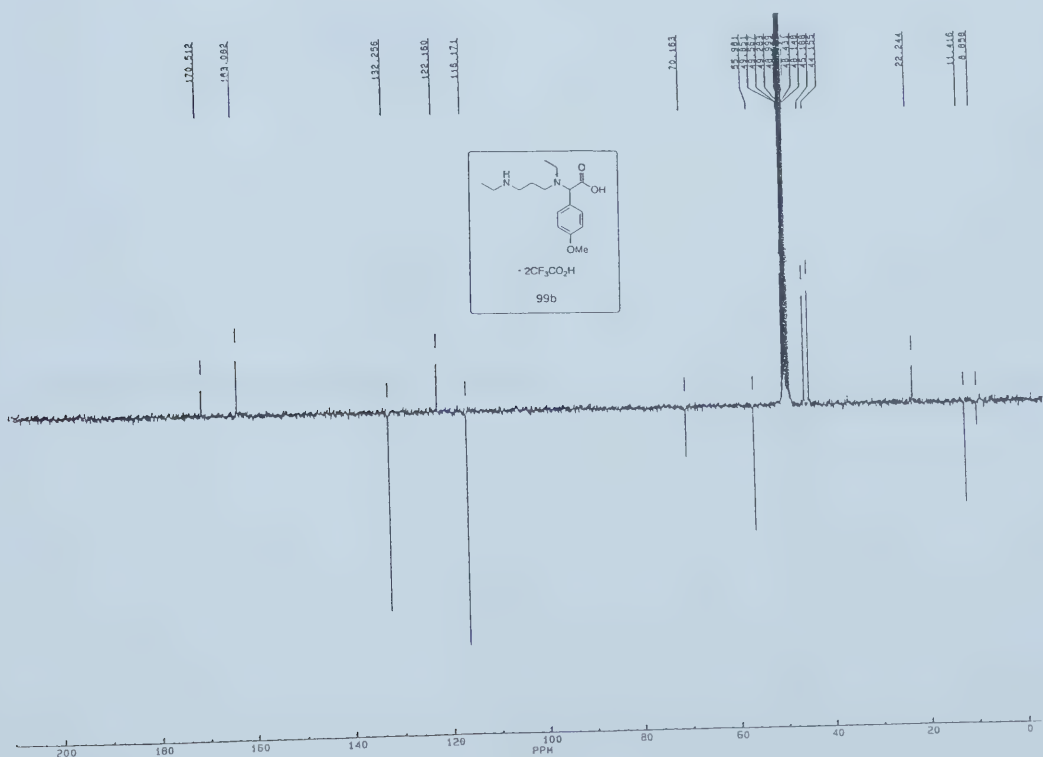
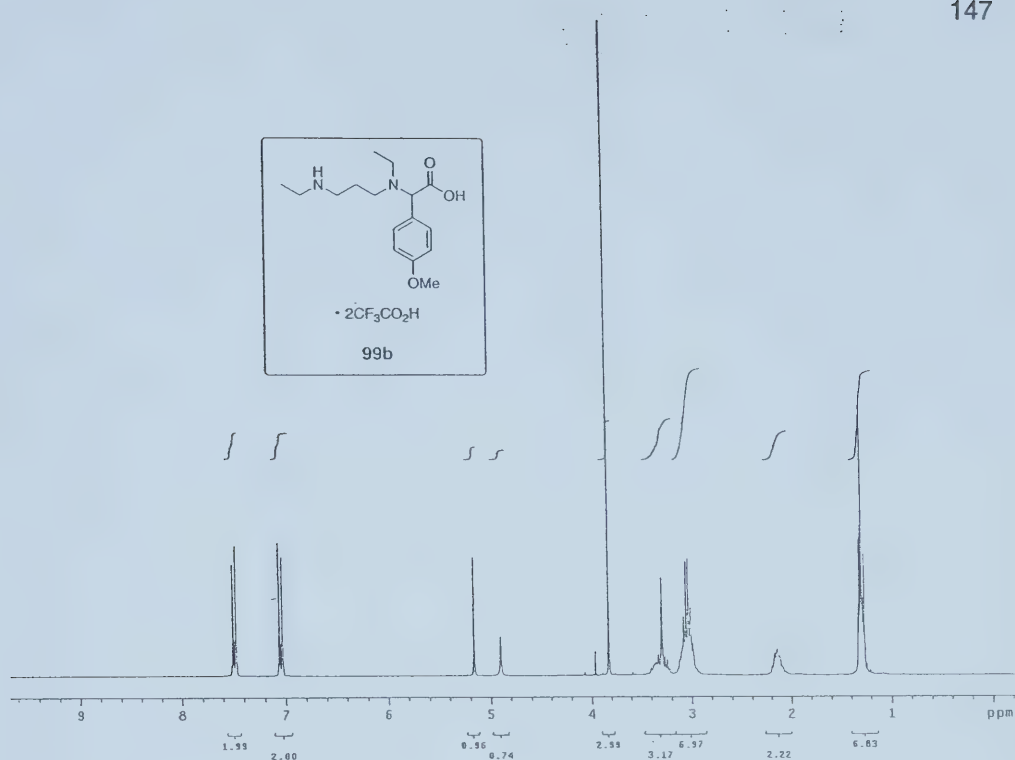




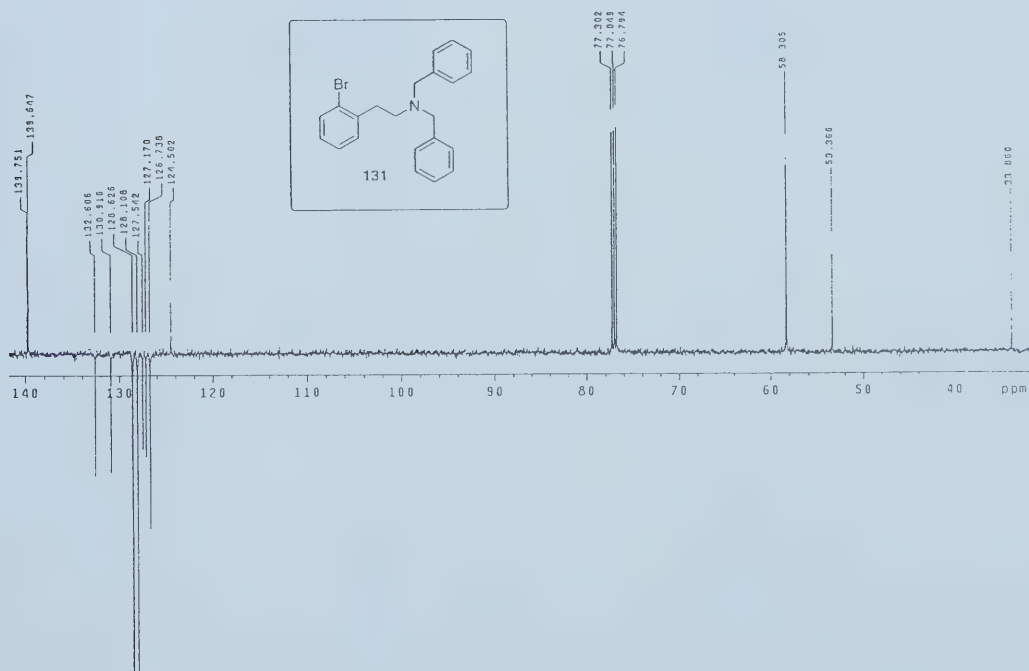
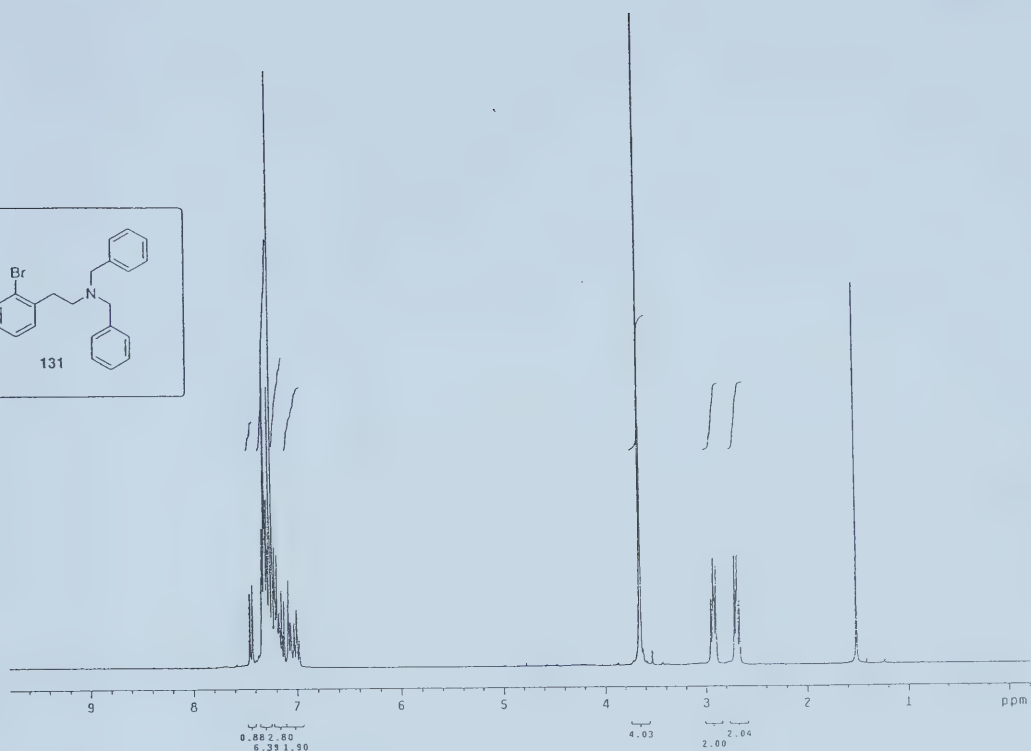
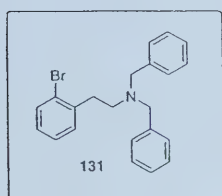


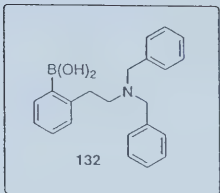












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